

LYMPHOMA

(a part of the group of tumors of the hematopoietic and lymphoid tissues)

LECTURE IN INTERNAL MEDICINE FOR IV COURSE STUDENTS

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Plan of the lecture

- Lymphoma' modern understanding
- Hodgkin lymphomas (HL), non-Hodgkin lymphomas (NHL) and Multiple myeloma
 - Definition
 - Epidemiology
 - Classification
 - Risk Factors and etiology
 - Mechanisms
 - Classification
 - Clinical presentation
 - Diagnosis
 - Treatment
 - Prognosis
 - Prophylaxis
 - Abbreviations
 - Diagnostic guidelines

Lymphoma' modern understanding

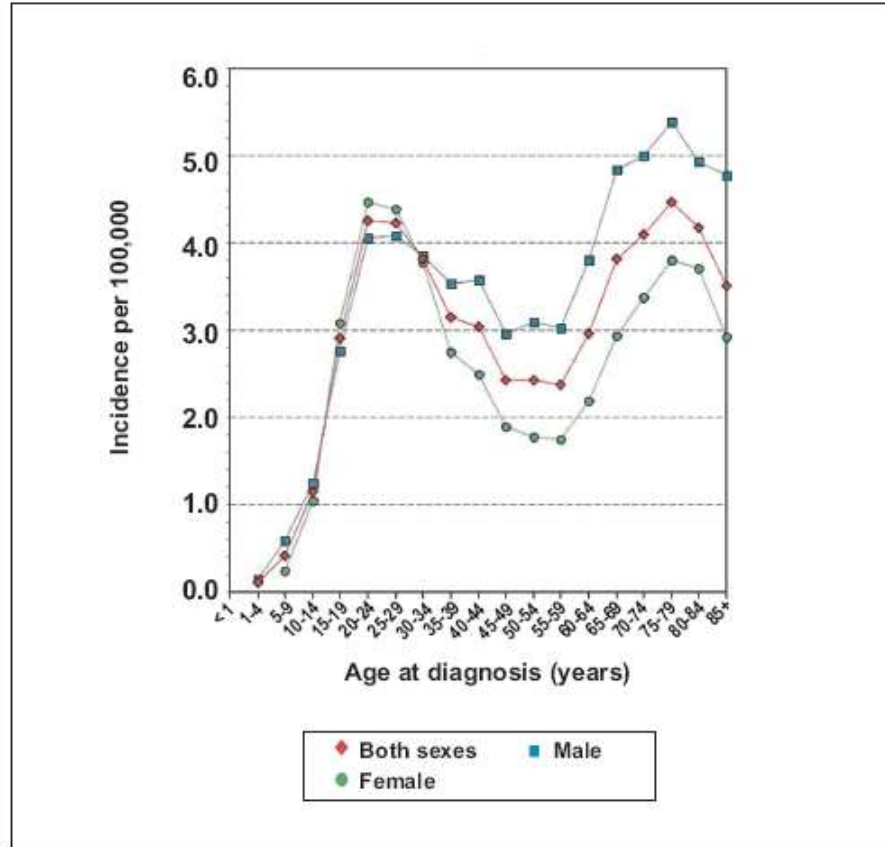
- Lymphoma is any of a group of blood cell tumors that develop from lymphatic cells with the enlarged lymph nodes and signs and symptoms that may include enlarged lymph nodes, fever, night drenching sweats, unintended weight loss, itching, and feeling tired
- The two main categories of lymphomas are Hodgkin lymphomas (HL) and the non-Hodgkin lymphomas (NHL)
- The World Health Organization (WHO) includes two other categories as types of lymphoma: multiple myeloma and immunoproliferative diseases

HODGKIN LYMPHOMA

Hodgkin lymphoma (HL): definition

- Hodgkin (Hodgkin's) lymphoma or Hodgkin's disease, is a type of the most curable forms of lymphoma, in which cancer originates from a specific type of white blood cells called lymphocytes
- Hodgkin Lymphoma is named for Dr. Thomas Hodgkin, who first noted a trend of cancer cases in the lymph nodes in 1832
- The disease was called Hodgkin's disease until it was officially renamed Hodgkin lymphoma in the late 20th century

Hodgkin lymphoma (HL): epidemiology

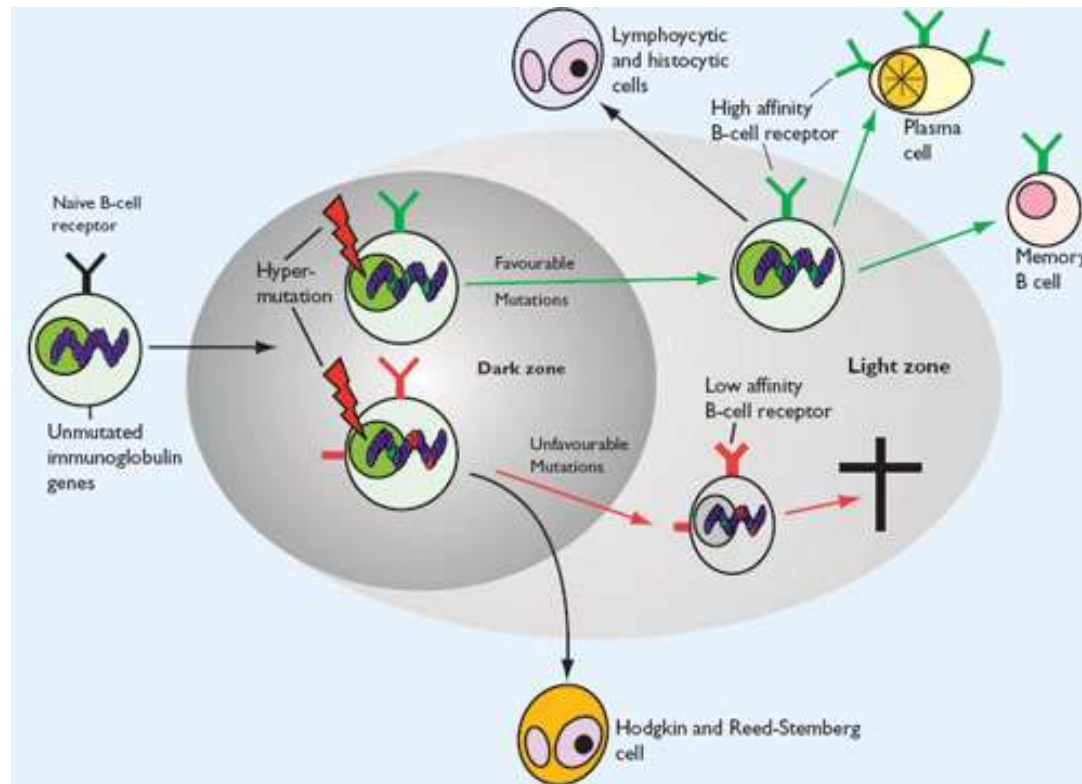


Incidence of Hodgkin Lymphoma in the United States, 2000-2005, by age: an age-related bimodal incidence pattern in HL persists

Hodgkin lymphoma (HL): risk factors and etiology

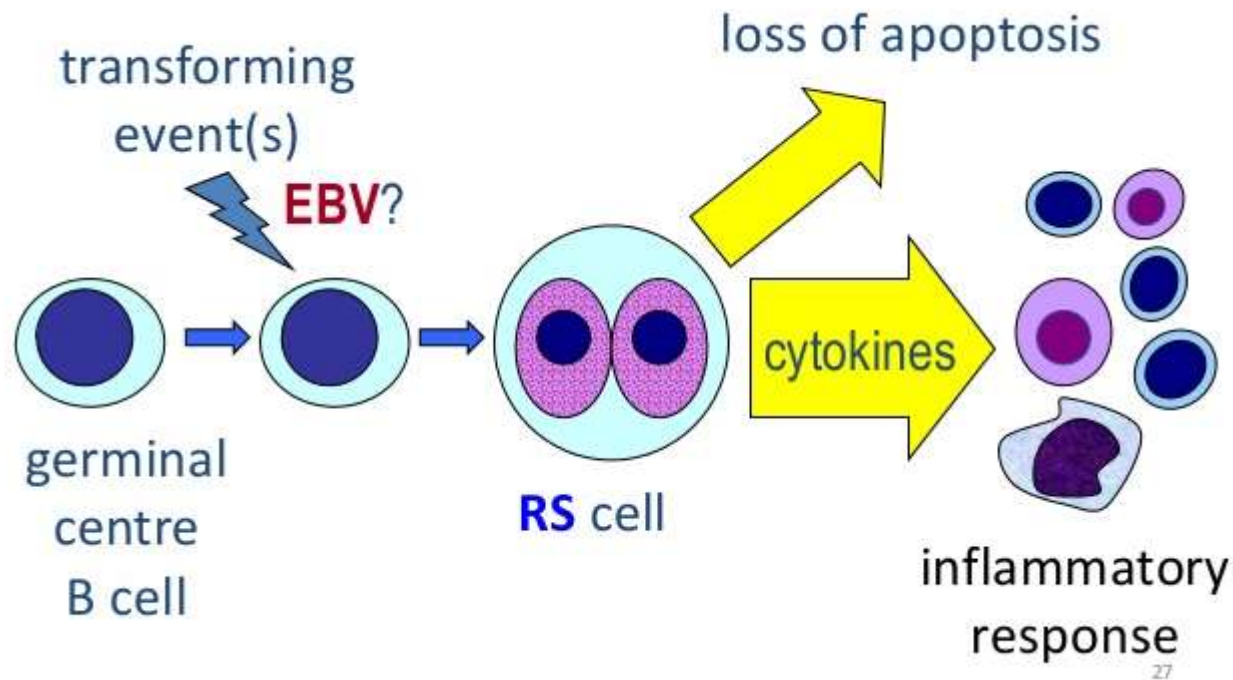
- Epstein-Barr virus infection/mononucleosis (sometimes called *mono* for short)
- Age (HL is most common in early adulthood (ages 15 to 40, especially in a person's 20s) and in late adulthood (after age 55))
- Gender (HD occurs slightly more often in males than in females)
- Geography (HD is most common in the United States, Canada, and northern Europe, and is least common in Asian countries)
- Family history (brothers and sisters of young people with HD have a higher risk for Hodgkin disease)
- Socioeconomic status (the risk is greater in people with a higher socioeconomic background)
- HIV infection (the risk is increased in people infected with HIV)
- In most cases, the etiology of HL is unknown

Hodgkin lymphoma (HL): mechanisms 1



The germinal-center derivation of Hodgkin and Reed-Sternberg cells in classic HL and lymphomatic and histiocytic cells in nodular lymphocyte-predominant HL

Hodgkin lymphoma (HL): mechanisms 2



A possible model of pathogenesis

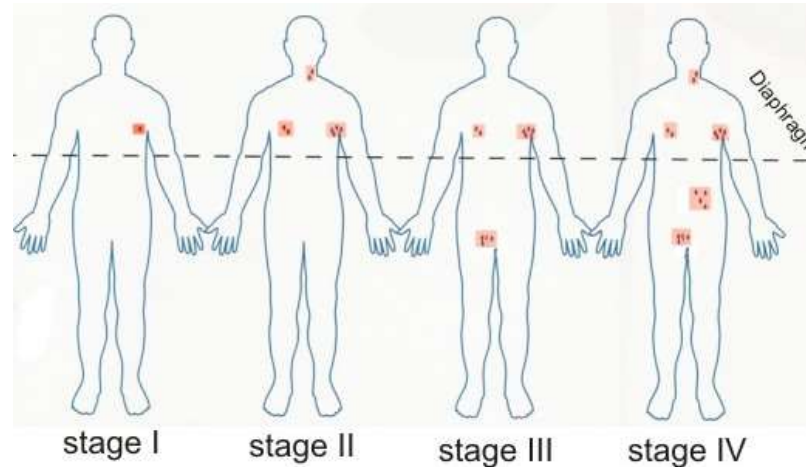
Hodgkin lymphoma (HL): classification

Four pathologic subtypes of HL based upon Reed–Sternberg cell morphology and the composition of the reactive cell infiltrate seen in the lymph node biopsy

Name	Description
Nodular sclerosing	Is the most common subtype and is composed of large tumor nodules showing scattered lacunar classical RS cells set in a background of reactive lymphocytes, eosinophils and plasma cells with varying degrees of collagen fibrosis/sclerosis
Mixed-cellularity subtype	Is a common subtype and is composed of numerous classic RS cells admixed with numerous inflammatory cells including lymphocytes, histiocytes, eosinophils, and plasma cells without sclerosis
Lymphocyte-rich	Is a rare subtype, show many features which may cause diagnostic confusion with nodular lymphocyte predominant B-cell Non-Hodgkin's Lymphoma (B-NHL)
Lymphocyte depleted	Is a rare subtype, composed of large numbers of often pleomorphic RS cells with only few reactive lymphocytes which may easily be confused with diffuse large cell lymphoma
Unspecified	

Hodgkin lymphoma (HL): classification

the Ann Arbor staging classification scheme



I - is involvement of a single lymph node region (I) (mostly the cervical region) or single extralymphatic site

II - is involvement of two or more lymph node regions on the same side of the diaphragm or of one lymph node region and a contiguous extralymphatic site

III - is involvement of lymph node regions on both sides of the diaphragm, which may include the spleen and/or limited contiguous extralymphatic organ or site

IV - is disseminated involvement of one or more extralymphatic organs

Hodgkin lymphoma (HL): clinical presentation 1

- The painless enlargement of one or more lymph nodes, or lymphadenopathy
- Itchy skin
- Night sweats
- Red-coloured patches, easy bleeding and petechiae (low platelet count)
- Cyclical high-grade (Pel-Ebstein or simply P-E) fever
- Unexplained weight loss
- Splenomegaly in about 30% of cases
- Hepatomegaly in about 5% of cases
- Pain following alcohol consumption
- Lower back pain
- Nephrotic syndrome

Hodgkin lymphoma (HL): clinical presentation 2



Lump in Neck

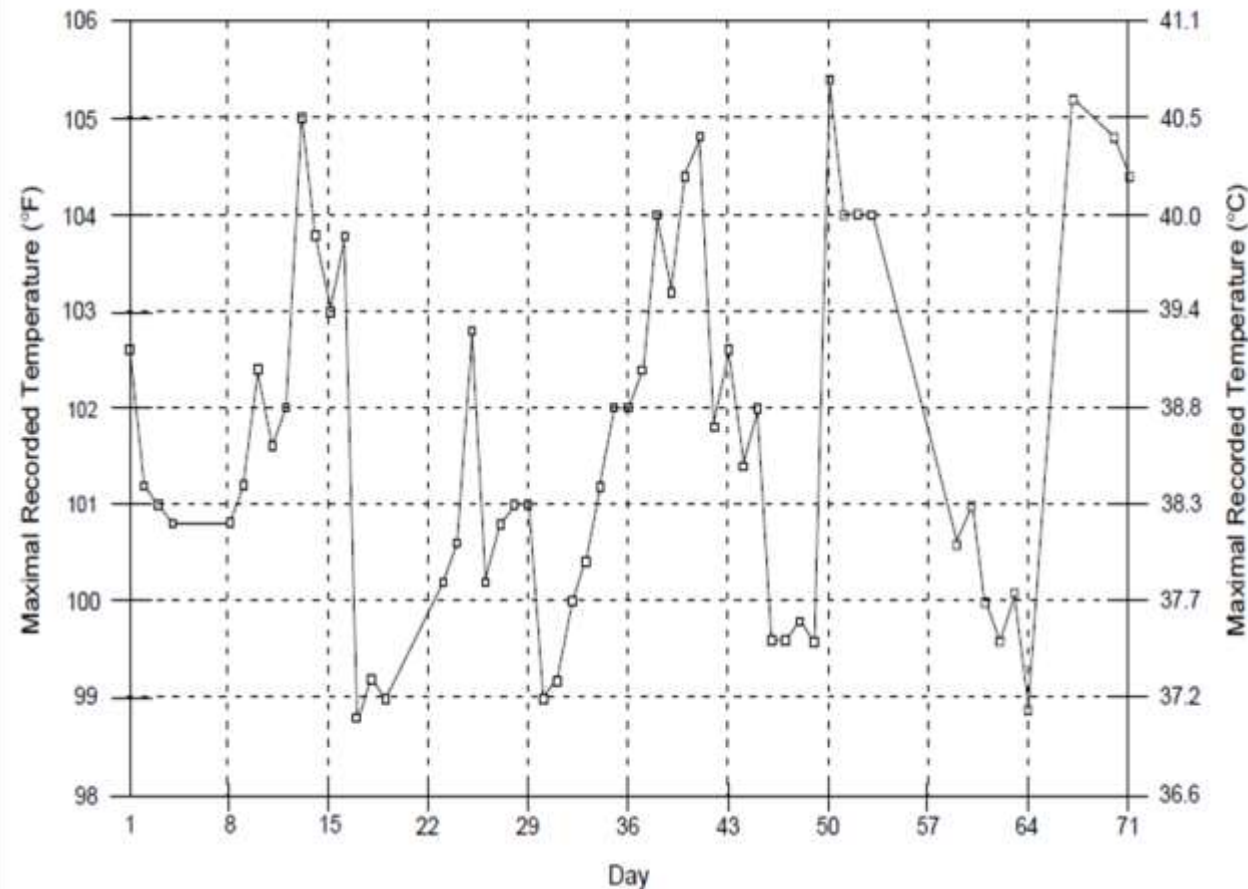


Itchy skin



On the left side of the patient's neck
enlarged lymph **node**

Hodgkin lymphoma (HL): clinical presentation 3

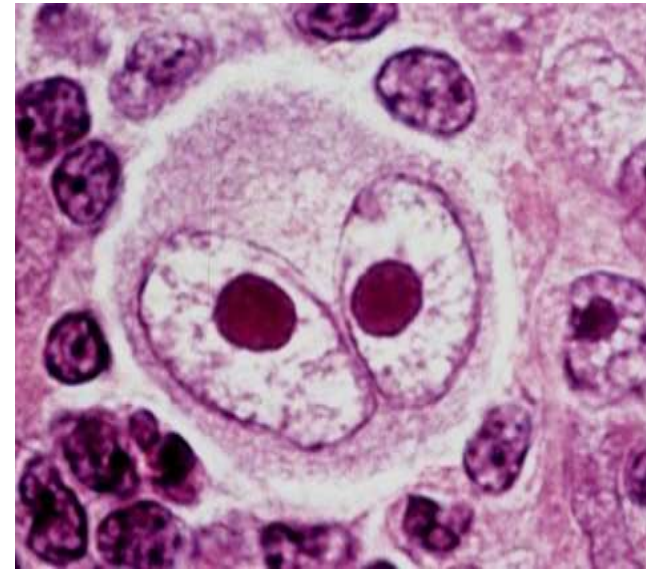
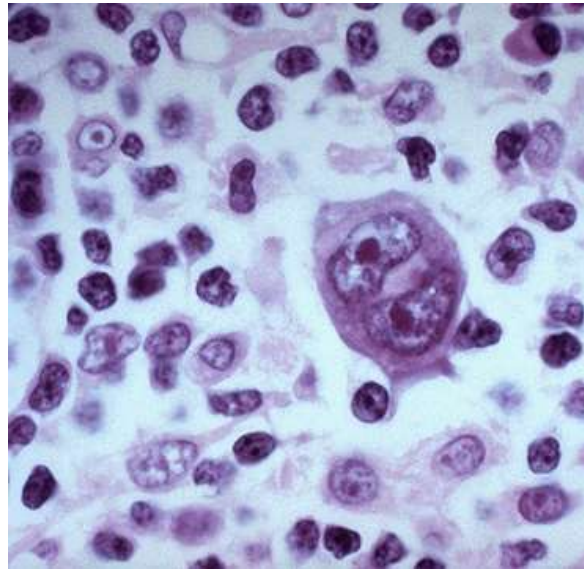
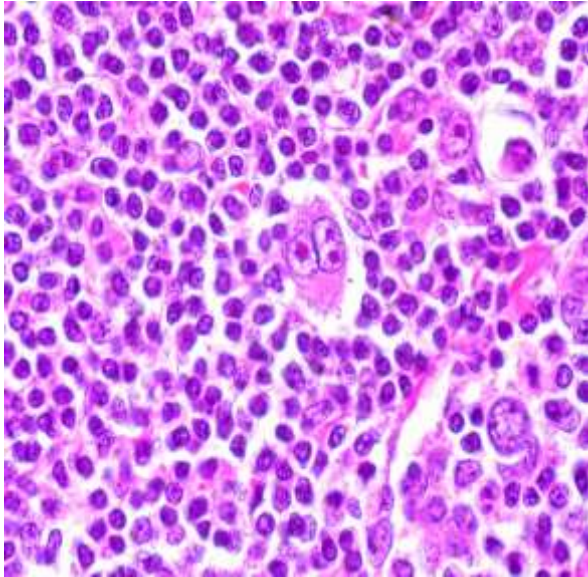


Pel-Ebstein Fever

Hodgkin lymphoma (HL): diagnosis 1

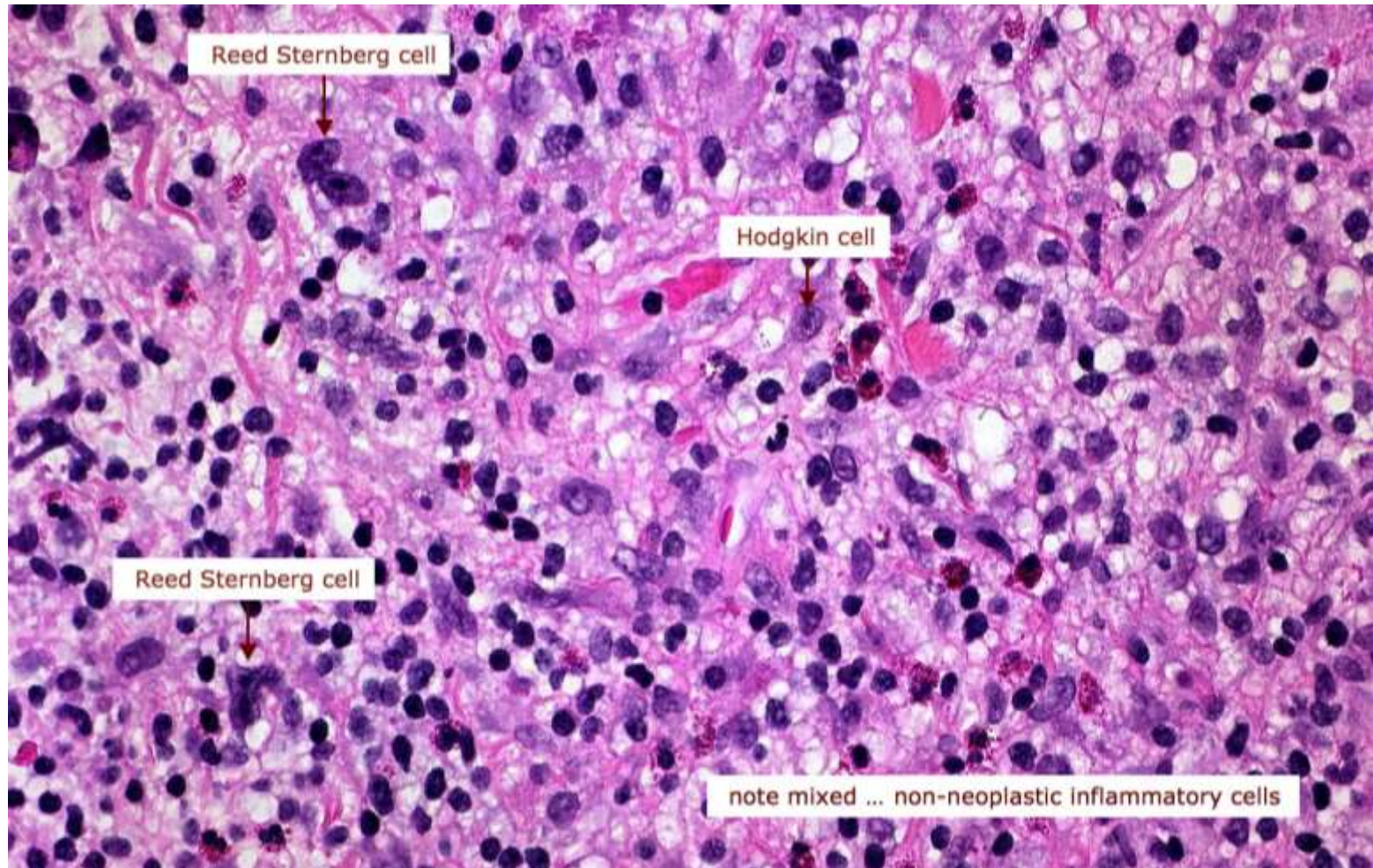
- HL must be distinguished from non-cancerous causes of lymph node swelling and from other types of cancer
- Definitive diagnosis is by lymph node biopsy with microscopic examination:
 - effacement of the lymph node architecture by scattered large malignant Reed-Sternberg cells (RSC) admixed within a reactive cell infiltrate of lymphocytes, histiocytes, eosinophils, and plasma cells
 - RSC are identified as large often bi-nucleated cells with prominent nucleoli and an unusual CD45-, CD30+, CD15+/- immunophenotype
 - in 50% of cases, the RSC are infected by the Epstein–Barr virus
 - the cell histology in HL is not as important as it is in non-Hodgkin's lymphoma
- Blood tests are performed to assess function of major organs and to assess safety for chemotherapy
- Positron emission tomography is used to detect small deposits that are not shown on CT scanning

Hodgkin lymphoma (HL): diagnosis 2



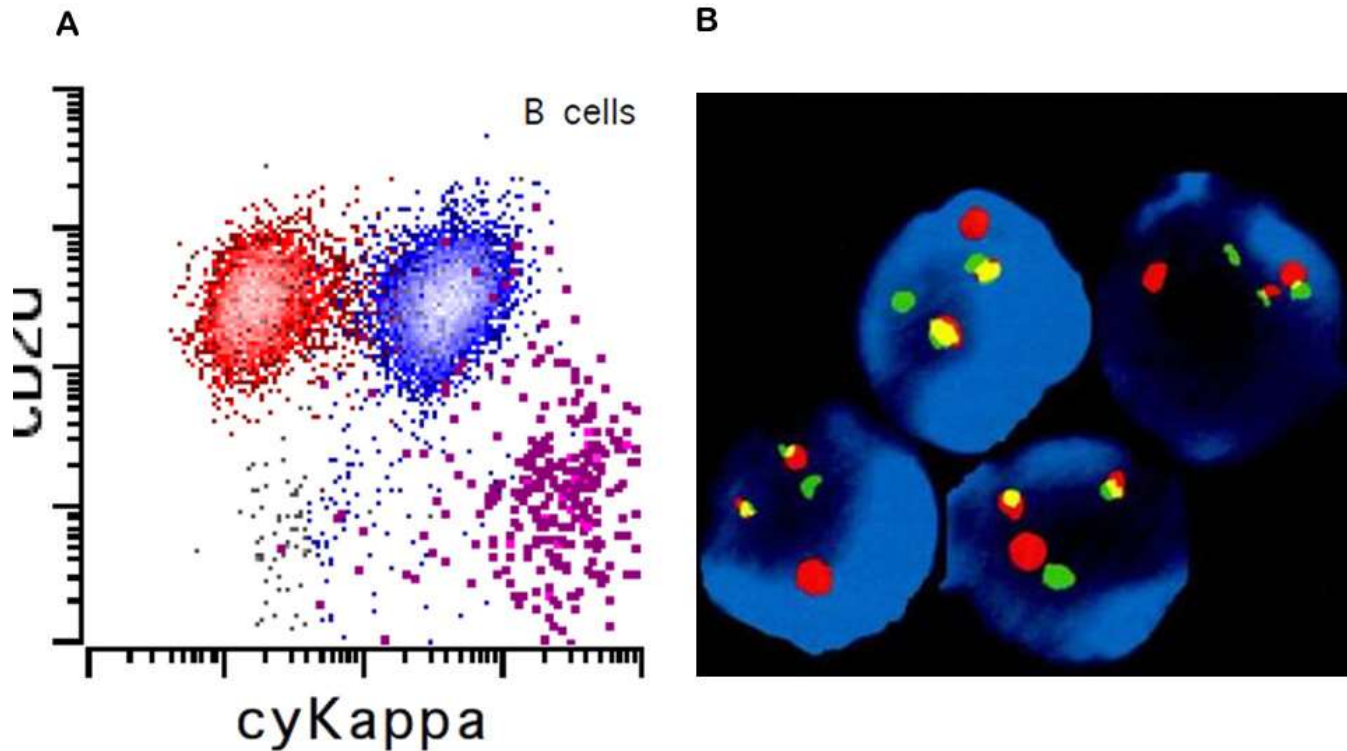
Reed-Sternberg cells

Hodgkin lymphoma (HL): diagnosis 3



Reed-Sternberg cells

Hodgkin lymphoma (HL): diagnosis



A) Flow cytometric immunophenotyping identifies subtle involvement by lymphoma in a background of benign cells (red and blue cells) B): fluorescence in situ hybridization (FISH) is one of the laboratory methods for accurate classification of lymphoma

Hodgkin lymphoma (HL): treatment

- Treatment is tailored to HL type, disease stage, and an assessment of the risk of resistant disease
- Patients with early stage disease are effectively treated with radiation therapy or chemotherapy: adding localised radiation therapy after the chemotherapy regimen controls the tumors better and provides a better chance for survival than chemotherapy alone
- Patients of any stage with a large mass in the chest are usually treated with combined chemotherapy and radiation therapy, and stem cell transplantation
- Radiation oncologists typically use external beam radiation therapy
- The high cure rates and long survival of many patients has led to a high concern with late adverse effects of treatment, including cardiovascular disease and second malignancies such as acute leukemias, lymphomas, and solid tumors within the radiation therapy field

Hodgkin lymphoma (HL): prognosis

- Treatment of HL has been improving over the past few decades
- New types of chemotherapy have indicated higher survival rates than have previously been seen, and the 5-year survival rate for those patients with a favorable prognosis was 98%, while that for patients with worse outlooks was at least 85%

Hodgkin lymphoma (HL): clinical case 1

Ptosis

- Lymphomas predominantly affect the lymph nodes but can present at unusual sites, which are termed as extranodal lymphomas
- Involvement of the ocular adnexa is an extremely uncommon occurrence, which is usually seen in patients with HL
- Doctors report herewith an unusual case of a 5-year-old child with HL and involvement of extraocular muscle leading to ptosis
- The child was managed by alternating cycles of cyclophosphamide, vincristine, procarbazine and prednisolone and adriamycin, bleomycin, vinblastine, and dacarbazine
- He had complete response to chemotherapy with resolution of ptosis

Hodgkin lymphoma (HL): clinical case 2

HL of the maxillary sinus

- The maxillary sinus is a rare anatomic site for HL
- Lymphoma in a patient who presents with disease in an unusual site and without lymphadenopathy is difficult to diagnose
- Doctors report the case of a 60-year-old woman who presented with nasal congestion and obstruction
- Examination revealed an abnormal-appearing mucosa involving the maxillary sinus
- The treatment commonly includes chemotherapy and radiotherapy, which yield excellent outcomes

Hodgkin lymphoma (HL): clinical case 3a

Distinguish cutaneous Hodgkin lymphoma from histopathologic imitators

- In lymph nodes, HL can be distinguished from non-Hodgkin lymphoma (NHL) by the presence of Hodgkin and Reed-Sternberg cells that co-express CD30 and CD15
- However, anaplastic large cell lymphoma (ALCL) and diffuse large B-cell lymphoma (DLBCL) can show identical features, and some cases of classical HL lack CD15 expression, rendering them difficult to differentiate from CD30-positive NHL
- The differential diagnosis of cutaneous HL similarly includes ALCL and DLBCL, and, additionally, tumors of mycosis fungoides
- The classical HL is of B-cell origin in virtually all cases, and shows at least focal weak expression of the B-cell marker PAX5 and often focal weak expression and no expression of the B-cell markers Oct-2 and BOB.1, respectively

Hodgkin lymphoma (HL): clinical case 3b

Distinguish cutaneous Hodgkin lymphoma from histopathologic imitators

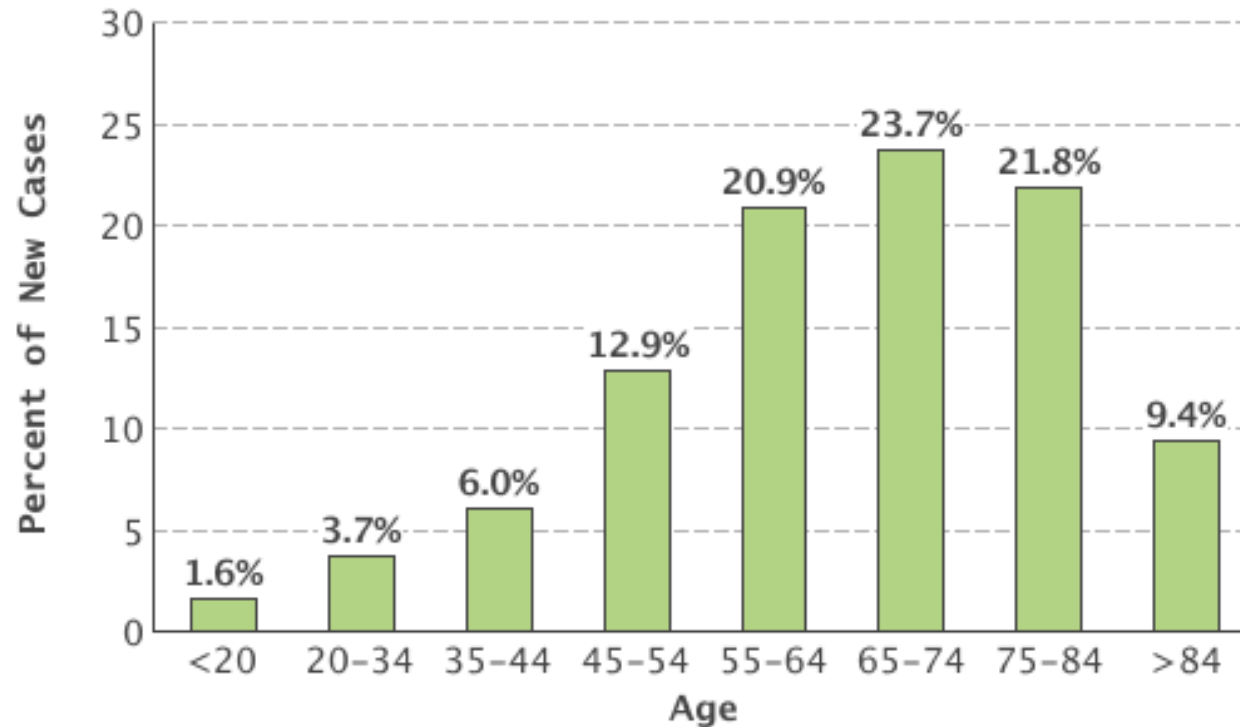
- All three of these markers are almost invariably absent in T-cell lymphomas and are strongly expressed in B-cell lymphomas
- Doctors report a 40-year-old man with classical HL who developed cutaneous nodules
- A biopsy from one revealed Hodgkin/Reed-Sternberg cells with a similar immunophenotype to the diagnostic lymph node biopsy, namely CD30+/CD15+, diffusely but weakly PAX5+, focally weakly Oct-2+ and lacking BOB.1 expression, thereby confirming a diagnosis of cutaneous HL
- This is the first report of the expression pattern of the combination of PAX5, Oct-2 and BOB.1 in the context of cutaneous involvement by Hodgkin lymphoma

NON-HODGKIN LYMPHOMA

Non-Hodgkin lymphoma (NHL): definition

- Non-Hodgkin lymphomas (Non-Hodgkin's lymphoma, Non-Hodgkin lymphomas, non-Hodgkin disease - NHL) are diverse group of blood cancers that include any kind of lymphomas except HL, and vary significantly in their severity, from slow growing to very aggressive types
- NHL affects the lymphatic system, generally develops in the lymph nodes and lymphatic tissues, and in some cases, involves bone marrow and blood

non-Hodgkin lymphoma (NHL): epidemiology



Percent of New Cases by Age Group: Non-Hodgkin Lymphoma

non-Hodgkin lymphoma (NHL): risk factors and etiology 1

There are many types of NHL, and some of the risk factors and etiology factors have been linked only to certain types:

- Getting older is a strong risk factor for NHL overall, with most cases occurring after 60s
- The risk is higher in men than in women, but there are certain types that are more common in women
- In the USA, whites are more likely than African Americans and Asian Americans to develop NHL
- NHL is more common in developed countries
- Some types of NHL that have been linked to specific infections are more common in certain parts of the world

non-Hodgkin lymphoma (NHL): risk factors and etiology 2

- Some chemicals (benzene and certain herbicides and insecticides) and some chemotherapy drugs may be linked with an increased risk of NHL
- Studies of survivors of atomic bombs and nuclear reactor accidents have shown they have an increased risk of developing several types of cancer, including NHL
- Patients treated with radiation therapy for some other cancers, have a slightly increased risk of developing NHL later in life
- People with weakened immune system including people infected with HIV have an increased risk for NHL
- Some genetic (inherited) syndromes can cause children to be born with a deficient immune system and a higher risk of developing NHL

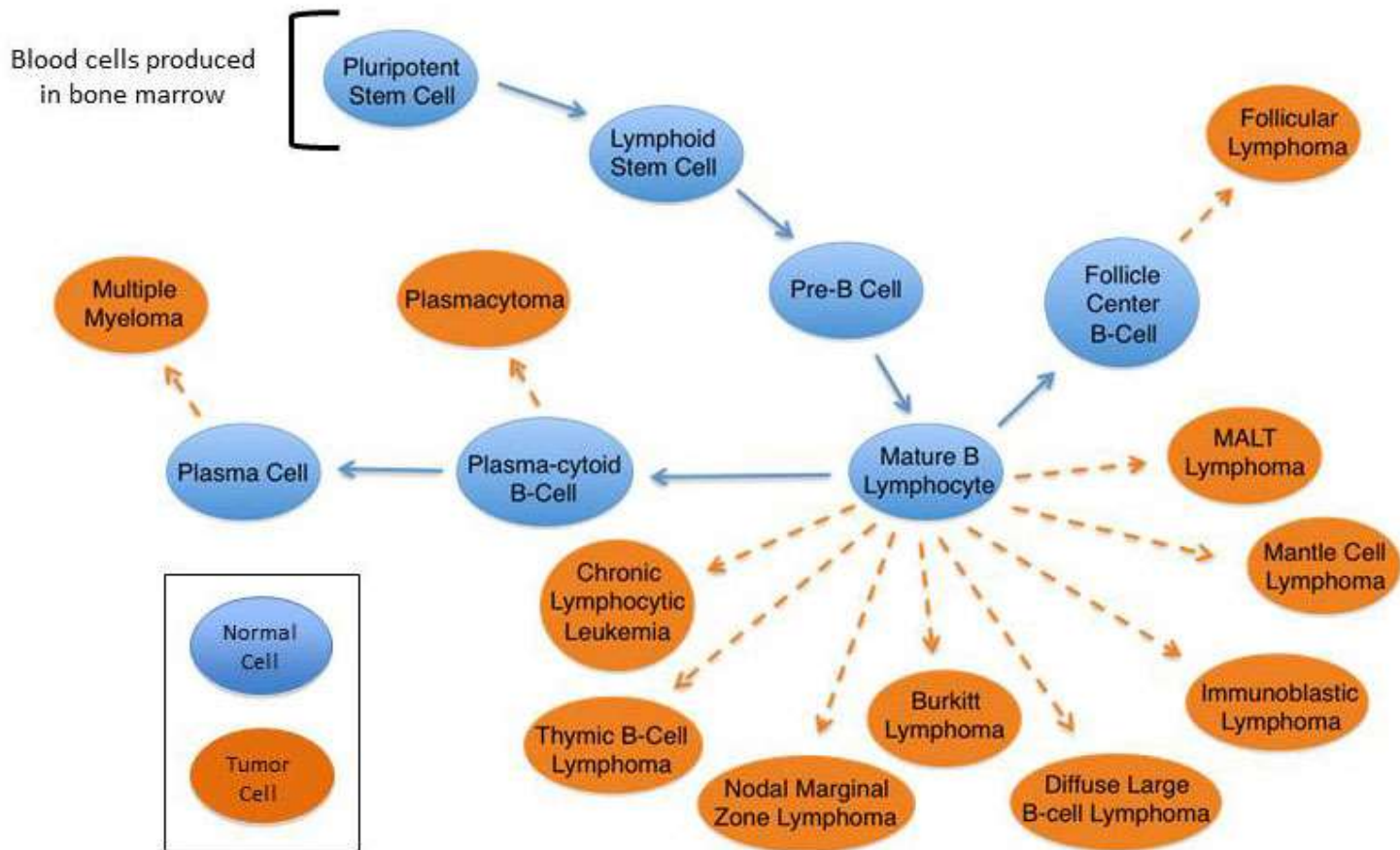
non-Hodgkin lymphoma (NHL): risk factors and etiology 3

- Some autoimmune diseases (rheumatoid arthritis, systemic lupus erythematosus, Sjogren disease, gluten-sensitive enteropathy, and others) have been linked with an increased rate of NHL
- Some types of infections may raise the risk of NHL in different ways
- Some viruses (the human T-cell leukemia/lymphoma virus (HTLV-1) and the Epstein-Barr virus (EBV) and human herpes virus 8 (HHV8)) can directly affect the DNA of lymphocytes, helping to transform them into cancer cells
- Some long-term infections (*Helicobacter pylori*, *Chlamydothila psittaci*, *Campylobacter jejuni*) may increase a person's risk of NHL by forcing their immune system to be constantly activated
- The hepatitis C virus (HCV) also can lead to the development of cancer, particularly hepatocellular carcinoma and non-Hodgkin lymphoma

non-Hodgkin lymphoma (NHL): risk factors and etiology 4

- Some studies have suggested that being overweight or obese may increase your risk of NHL
- Other studies have suggested that a diet high in fat and meats may raise NHL risk
- Some women develop anaplastic large cell lymphoma in the scar tissue around their breast implants

Non-Hodgkin lymphoma (HL): mechanisms



NHL does not involve Reed-Sternberg cells

non-Hodgkin lymphoma (NHL): classification 1

The three most commonly used classification schemas for NHL are as follows:

- National Cancer Institute's Working Formulation (IWF) classified and grouped NHL by morphology and clinical behavior (i.e., low, intermediate, or high grade) with 10 subgroups labeled A to J
- Revised European-American Classification of Lymphoid Neoplasms (REAL) attempted to apply immunophenotypic and genetic features in identifying distinct clinicopathologic NHL entities
- World Health Organization (WHO) classification divides NHL into two groups: those of B-cell origin and those of T-cell/natural killer (NK)–cell origin

non-Hodgkin lymphoma (NHL): classification 2

National Cancer Institute's Working Formulation (IWF) of NHL by clinical behavior:

- Low-grade NHL subtypes:
 - A. Small lymphocytic, consistent with chronic lymphocytic leukemia
 - B. Follicular, predominantly small-cleaved cell
 - C. Follicular, mixed small-cleaved, and large cell
- Intermediate-grade NHL subtypes:
 - D. Follicular, predominantly large cell
 - E. Diffuse, small-cleaved cell
 - F. Diffuse mixed, small and large cell
 - G. Diffuse, large cell, cleaved, or noncleaved cell
- High-grade NHL subtypes
 - H. Immunoblastic, large cell
 - I. Lymphoblastic, convoluted, or nonconvoluted cell
 - J. Small noncleaved-cell, Burkitt, or non-Burkitt

non-Hodgkin lymphoma (NHL): classification 3

Revised European-American Classification of Lymphoid Neoplasms (REAL):

- The classification is comprehensive, including Hodgkin's and non-Hodgkin's lymphomas, as well as the lymphoid leukemias
- Three major categories of lymphoid neoplasia were agreed upon: B-cell, T/natural killer (NK)-cell, and Hodgkin's disease
- Within each of the major disease categories, the consensus panel recognized "definite," "provisional," and "unclassifiable" (not further classifiable) subsets
- The classification is intended to be a flexible framework, subject to modification as new information and better understanding of the pathobiology ensues

non-Hodgkin lymphoma (NHL): classification 4

World Health Organization (WHO) classification:

B-cell neoplasms are as follows: chronic lymphocytic leukemia/small lymphocytic lymphoma, prolymphocytic leukemia, lymphoplasmacytic lymphoma/immunocytoma, Mantle cell lymphoma, follicular lymphoma, extranodal marginal zone B-cell lymphoma of mucosa-associated lymphatic tissue (MALT) type, nodal marginal zone B-cell lymphoma (\pm monocytoid B cells), splenic marginal zone lymphoma (\pm villous lymphocytes), hairy cell leukemia, plasmacytoma/plasma cell myeloma, diffuse large B-cell lymphoma (DLBCL), Burkitt lymphoma

non-Hodgkin lymphoma (NHL): classification 5

World Health Organization (WHO) classification:

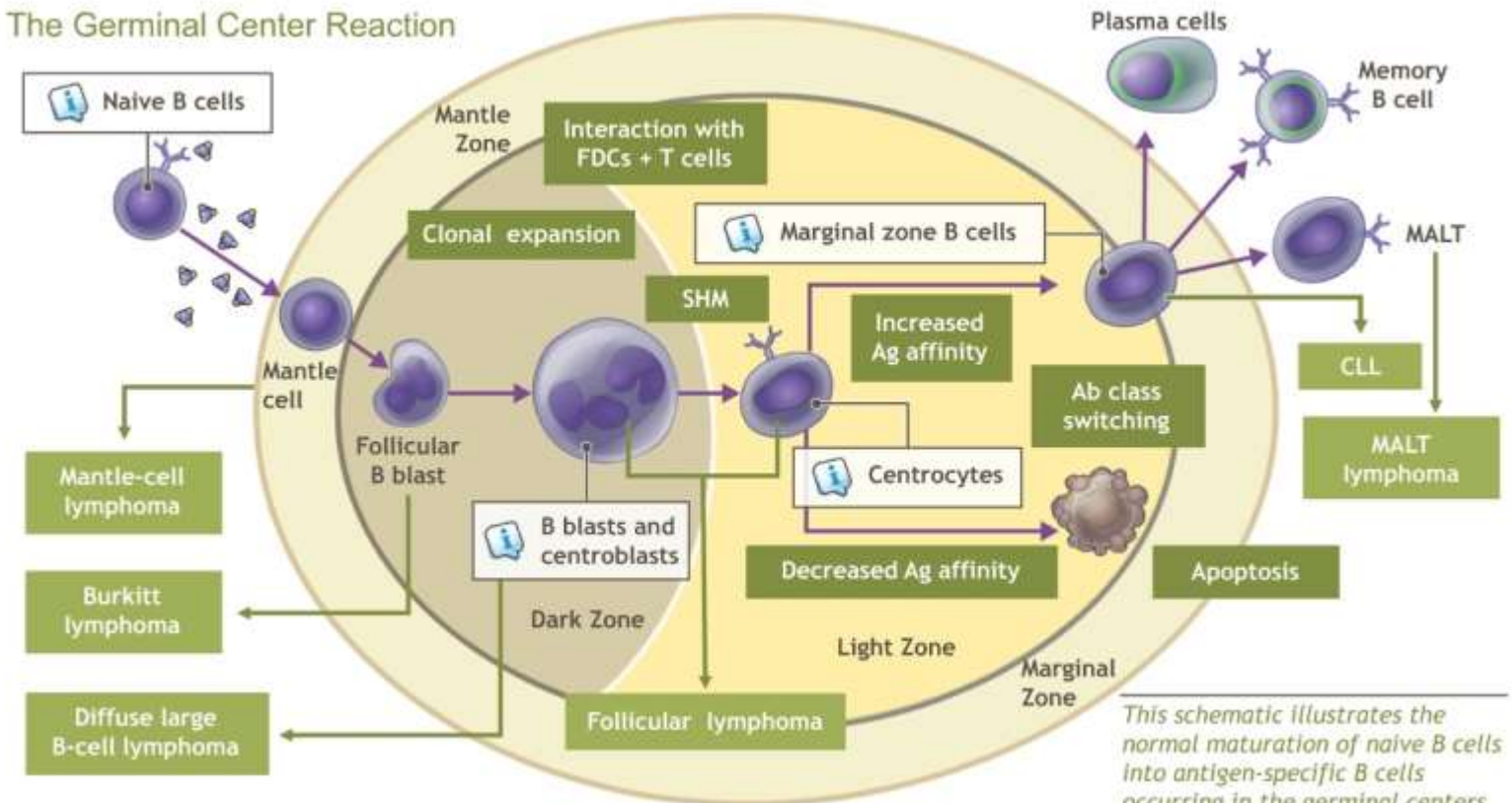
Peripheral T-cell and NK-cell neoplasms are as follows: T-cell chronic lymphocytic leukemia/prolymphocytic leukemia, T-cell granular lymphocytic leukemia, mycosis fungoides/Sézary syndrome, peripheral T-cell lymphoma not otherwise characterized, hepatosplenic gamma/delta T-cell lymphoma, subcutaneous panniculitis-like T-cell lymphoma, angioimmunoblastic T-cell lymphoma, extranodal T-/NK-cell lymphoma, nasal type, enteropathy-type intestinal T-cell lymphoma, adult T-cell lymphoma/leukemia (human T-lymphotrophic virus [HTLV] 1+), anaplastic large cell lymphoma, primary systemic type, anaplastic large cell lymphoma, primary cutaneous type, aggressive NK-cell leukemia

non-Hodgkin lymphoma (NHL): clinical presentation 1

- The clinical presentation of NHL varies tremendously depending upon the their type and the areas of involvement
- Some NHLs behave indolently with lymphadenopathy waxing and waning over years, and others are highly aggressive, resulting in death within weeks if left untreated
- Indolent NHL are often insidious, presenting only with slow growing lymphadenopathy, hepatomegaly, splenomegaly, or cytopenias
- Aggressive NHL commonly present acutely or subacutely with a rapidly growing mass, systemic B symptoms (i.e., fever, night sweats, weight loss), and/or elevated levels of serum lactate dehydrogenase and uric acid

non-Hodgkin lymphoma (NHL): clinical presentation 2

The Germinal Center Reaction



Select the "i" icons for information on the different types of cells.

Indolent NHL

non-Hodgkin lymphoma (NHL): clinical presentation 3



Peripheral adenopathy in indolent NHL

non-Hodgkin lymphoma (NHL): clinical presentation 4



Aggressive NHL

non-Hodgkin lymphoma (NHL): clinical presentation 5



Gingival appearance of patient with NHL

non-Hodgkin lymphoma (NHL): clinical presentation 6



Spleen, NHL: uniform multicentric involvement of the white pulp by a malignant lymphoma

non-Hodgkin lymphoma (NHL): clinical presentation 6

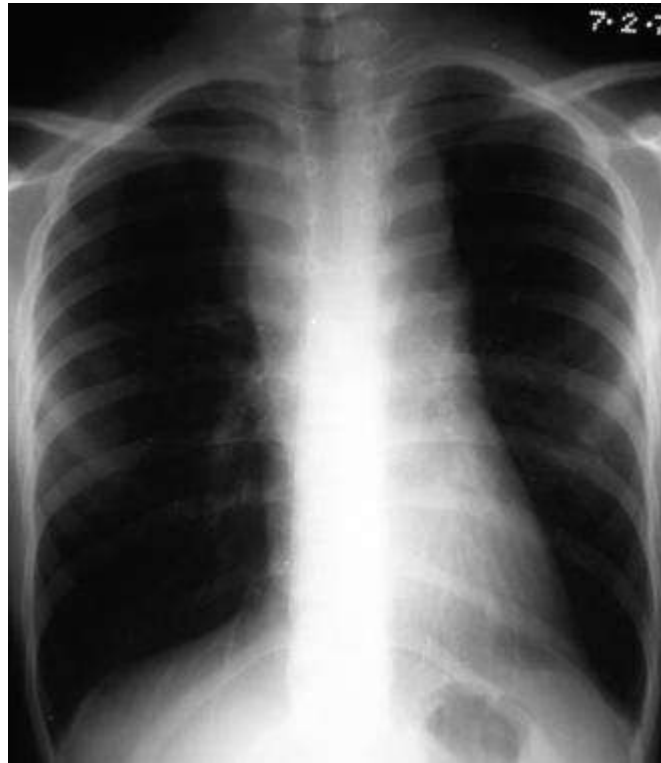


Cutaneous T-Cell NHL

non-Hodgkin lymphoma (NHL): diagnosis 1

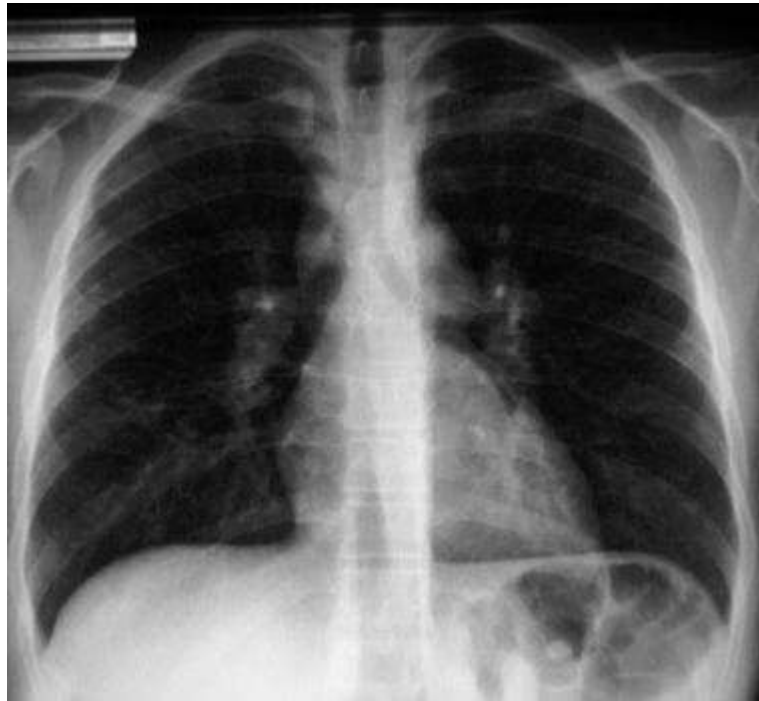
- NHL is diagnosed by a tissue biopsy of an enlarged, painless lymph node, without of an infection
- Patient will need some or all of the following tests depending on symptoms and the type of the NHL:
- Lymph node biopsy
- Imaging tests (X-rays, computed tomography (CT), positron emission tomography (PET), magnetic resonance imaging (MRI))
- Blood tests
- Bone marrow aspiration and biopsy
- Liver and kidney function tests
- Spinal tap (lumbar puncture)
- Immunophenotyping of cells from a lymph node, blood or bone marrow to determine what type of non-Hodgkin's lymphoma cells are present.
- Echocardiogram
- Pulmonary function test

non-Hodgkin lymphoma (NHL): diagnosis 2



Posteroanterior (PA) chest radiograph in a man with thoracic NHL shows mediastinal widening due to grossly enlarged right paratracheal and left paratracheal nodes

non-Hodgkin lymphoma (NHL): diagnosis 3



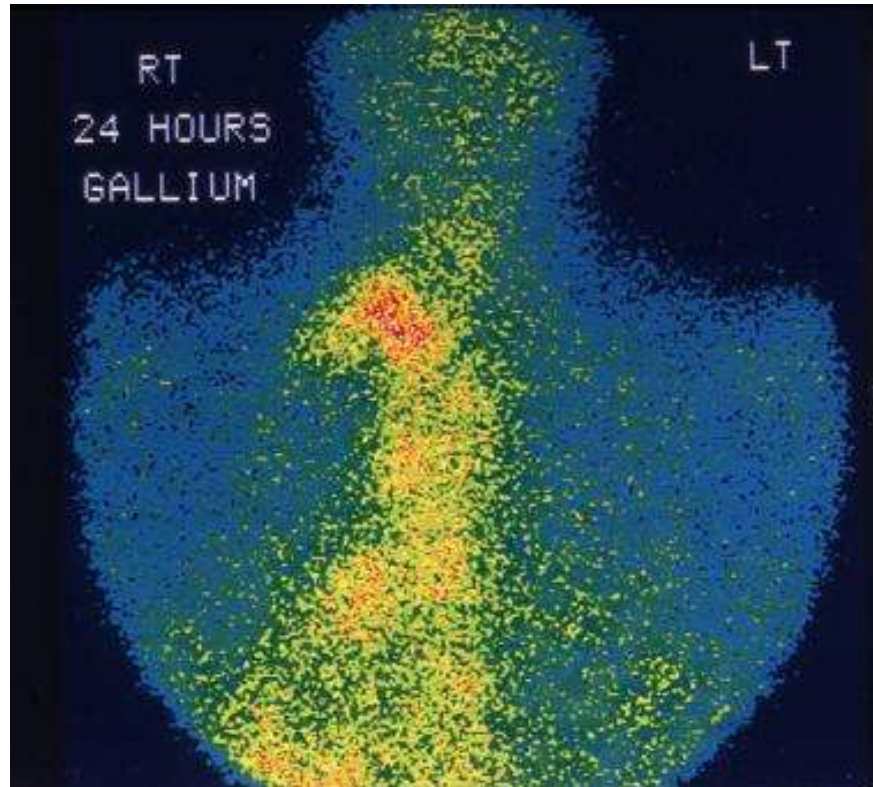
Posteroanterior (PA) chest radiograph in a 16-year-old male adolescent with thoracic NHL shows subtle enlargement of the lower paratracheal lymph nodes

non-Hodgkin lymphoma (NHL): diagnosis 4



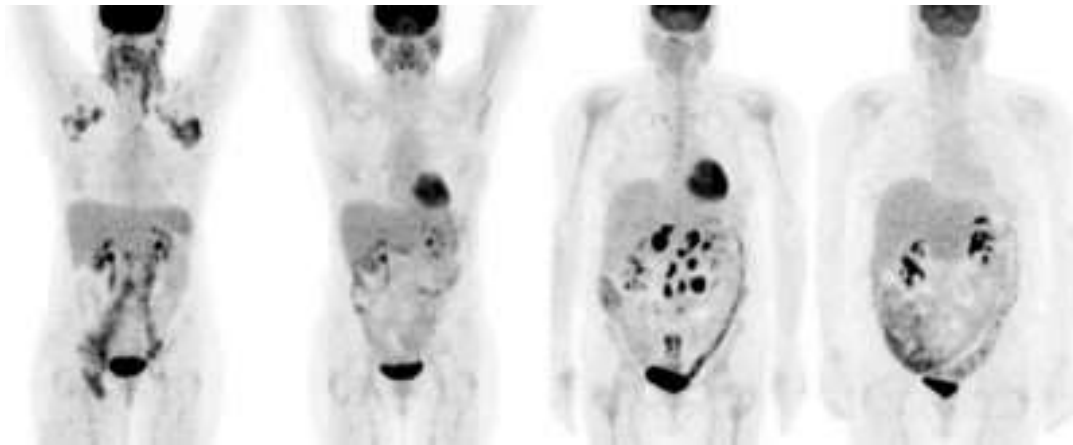
Posteroanterior chest radiograph shows a large mass in the right parahilar region extending into the right upper and middle zones, with silhouetting of the right pulmonary artery: smaller mass is seen in the periphery of the right lower zone, that did not respond to a trial of antibiotics; core-needle biopsy of the larger lesion revealed NHL deposits in the lung

non-Hodgkin lymphoma (NHL): diagnosis 5



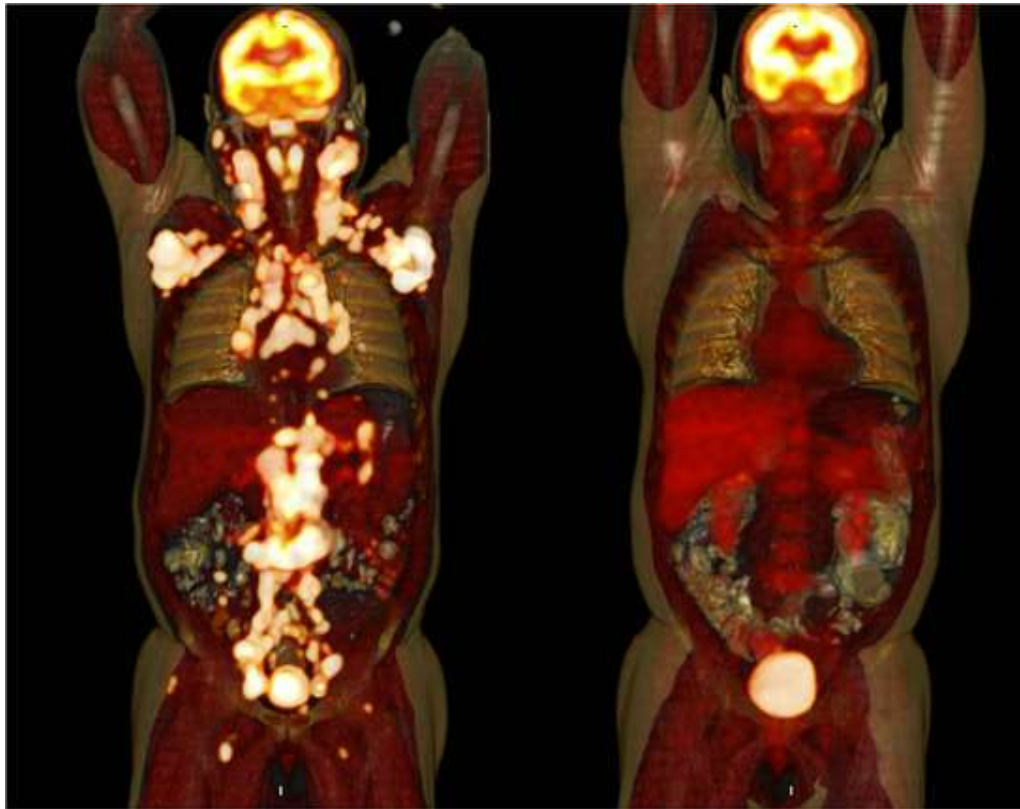
Extensive uptake in the mediastinal lymph nodes due to NHL

non-Hodgkin lymphoma (NHL): diagnosis 6



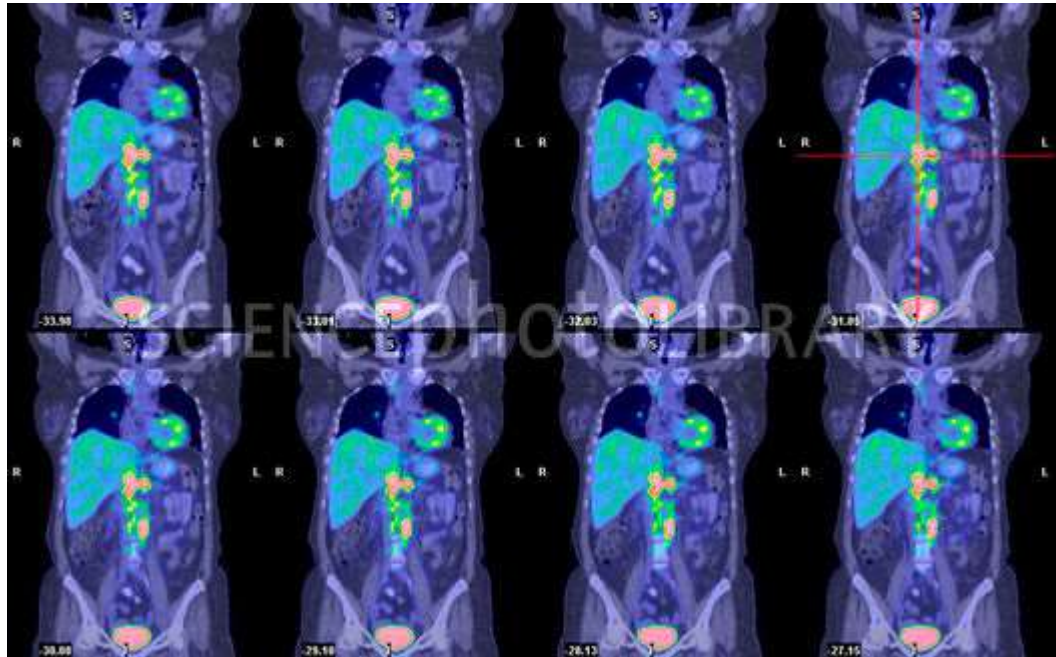
Two sets of before and after FDG-PET scans of two patients with NHL treated with Zevalin or Bexxar

non-Hodgkin lymphoma (NHL): diagnosis 7



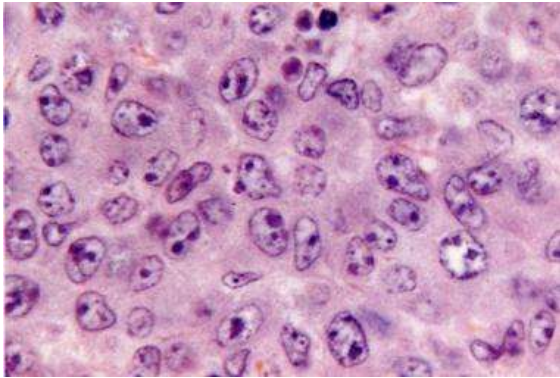
PET/CT images (coronal sections, display as virtual anatomy) using FDG of a patient with non-Hodgkin lymphoma before (left) and after (right) chemotherapy, showing complete response

non-Hodgkin lymphoma (NHL): diagnosis 8

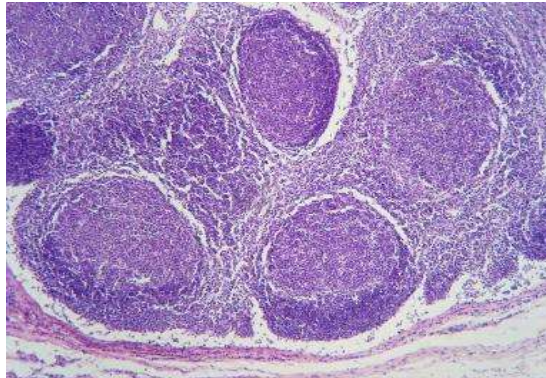


Coloured composite computed tomography (CT) and positron emission tomography (PET) scans of sections through a patient with growths in the abdomen and chest due to NHL

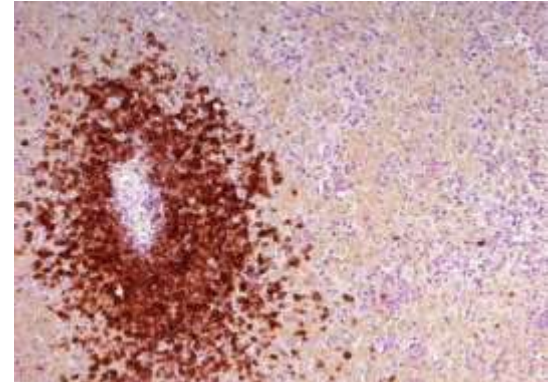
non-Hodgkin lymphoma (NHL): diagnosis 9



Diffuse large B-cell NHL



Aggressive NHL



Aggressive NHL

non-Hodgkin lymphoma (NHL): treatment

- The main types of treatment are chemotherapy (intravenously e.g. CVP (cyclophosphamide, vincristine, prednisolone) with monoclonal antibody drug rituximab, CHOP (cyclophosphamide, doxorubicin, vincristine and prednisolone), FAD (fludarabine, doxorubicin, dexamethasone), or FMD (fludarabine, mitoxantrone and dexamethasone), radiotherapy (often used as a local treatment), and biological (e.g. rituximab, ibritumomab, tositumomab, epratuzumab, alemtuzumab) therapy
- Some people may have surgery to remove a tumour or the spleen
- Sometimes high dose chemotherapy with a stem cell transplant may be used to try to increase the chance of curing NHL
- Some people need only one type of treatment and others need more than one

non-Hodgkin lymphoma (NHL): prognosis

- Survival rates for NHL vary widely, depending on the lymphoma type, stage, age of the patient, and other variables
- According to the American Cancer Society, the overall 5-year relative survival rate for patients with non-Hodgkin's lymphoma is 63% and the 10-year relative survival rate is 51%
- Survival rates for patients with NHL have greatly improved since the early 1990s, especially for patients under age 45
- Advances in treatment have contributed to this improvement

non-Hodgkin lymphoma (NHL): clinical case 1a

Primary pituitary NHL developed following surgery and radiation of a pituitary macroadenoma

- Primary central nervous system (CNS) NHL is a rarely encountered clinical entity
- There is present a case of a primary CNS diffuse large B-cell non-Hodgkin's lymphoma developed on a previously operated and irradiated pituitary macroadenoma
- 60-year-old woman presented with muscle weakness and eye lid ptosis
- Thirty years ago, she was diagnosed with a non-functioning pituitary macroadenoma requiring repeated incomplete operations and conventional radiotherapy and accompanied by partial anterior pituitary deficiency
- On admission, the magnetic resonance imaging (MRI) identified a pituitary sellar mass extending into the suprasellar region, compressing the optic chiasm and invading the left cavernous sinus

non-Hodgkin lymphoma (NHL): clinical case 1b

Primary pituitary NHL developed following surgery and radiation of a pituitary macroadenoma

- Following transsphenoidal surgery, the histological investigation revealed the presence of a diffuse large B-cell NHL without other loci from the systemic staging
- Following chemotherapy and despite a marked resolution of the neoplastic pituitary mass in the post-chemotherapy MRI scan, the patient's course was complicated with consciousness deterioration attributed to epileptic seizures and she died of a hospital acquired infection
- Clinicians should include primary CNS lymphoma in the differential diagnosis of an isolated invasive sellar mass
- The possible association of primary CNS lymphoma development with the history of operated and irradiated pituitary adenoma is herein discussed

non-Hodgkin lymphoma (NHL): clinical case 2

NHL of the ovary in a child with Ataxia-telangiectasia

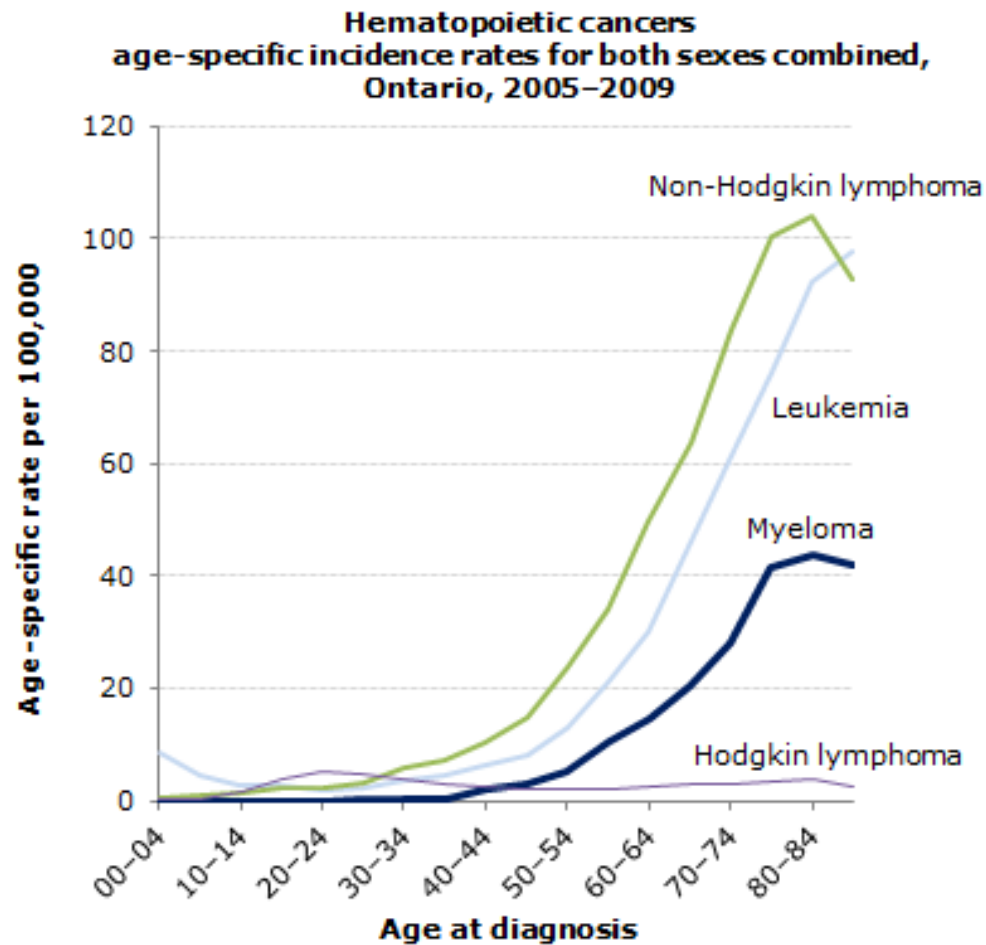
- Ataxia-telangiectasia is a multisystem, life-limiting, recessively inherited genetic disorder caused by mutations in the Ataxia-telangiectasia mutated gene
- It is characterized by the onset of changes in neurological and immunological development, organ maturation in childhood, as well as a high incidence of malignancies
- There is describe a case of an 11-year-old girl with a history of progressive ataxia and new finding of bilateral pelvic masses
- Given an elevated alpha-fetoprotein, the pre-operative working diagnosis was a malignant germ cell tumor
- Final ovarian pathology revealed a non-Hodgkin B-cell lymphoma with Burkitt-like morphology
- It is the first case of a primary ovarian non-Hodgkin B-cell lymphoma in a child with Ataxia-telangiectasia

MULTIPLE MYELOMA

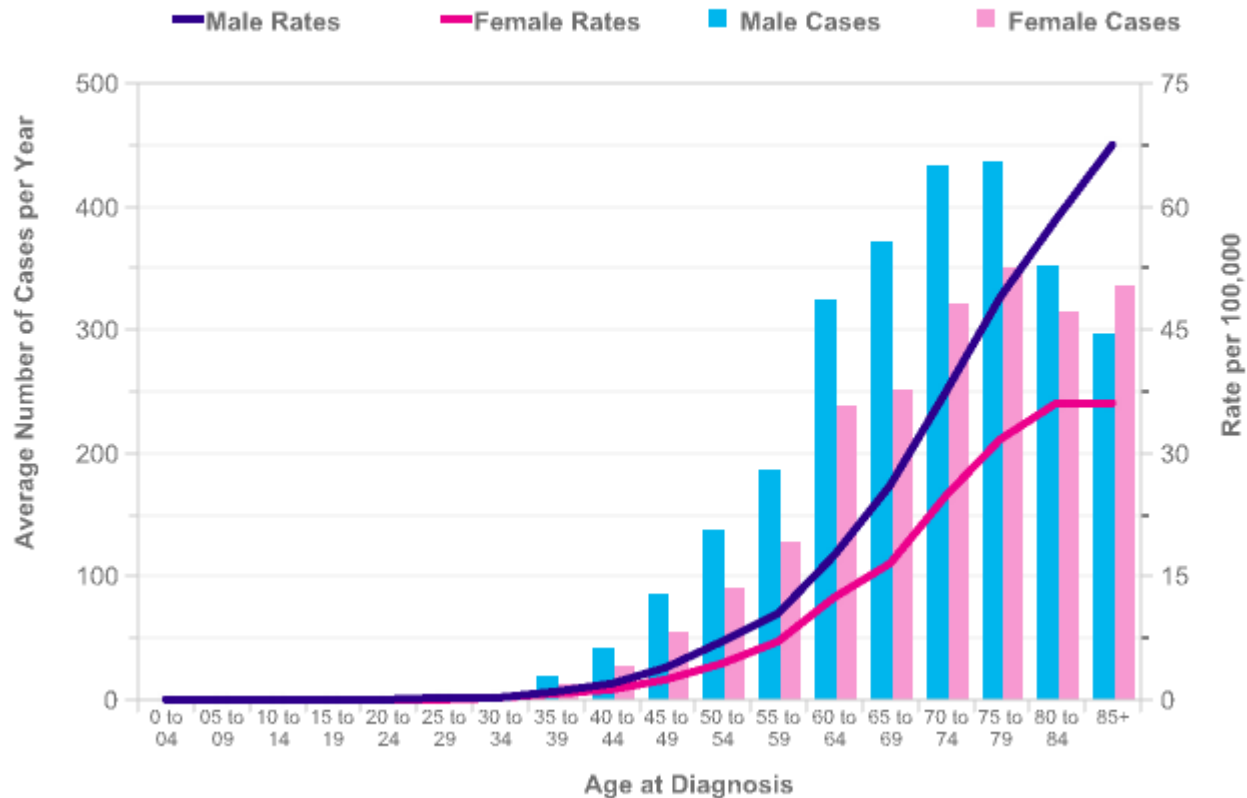
Multiple myeloma (MM): definition

- Multiple myeloma (plasma cell myeloma, myelomatosis, Kahler's disease - MM), is a cancer of plasma cells, in physiological conditions responsible for producing normal antibodies, wherein collections of their abnormal forms accumulate in the bone marrow and interfere with the normal blood cells
- In most cases of MM abnormal plasma cells produce a paraprotein, which can cause kidney failure
- Bone lesions in MM can lead to hypercalcemia (high blood calcium levels)

Multiple myeloma (MM): epidemiology 1

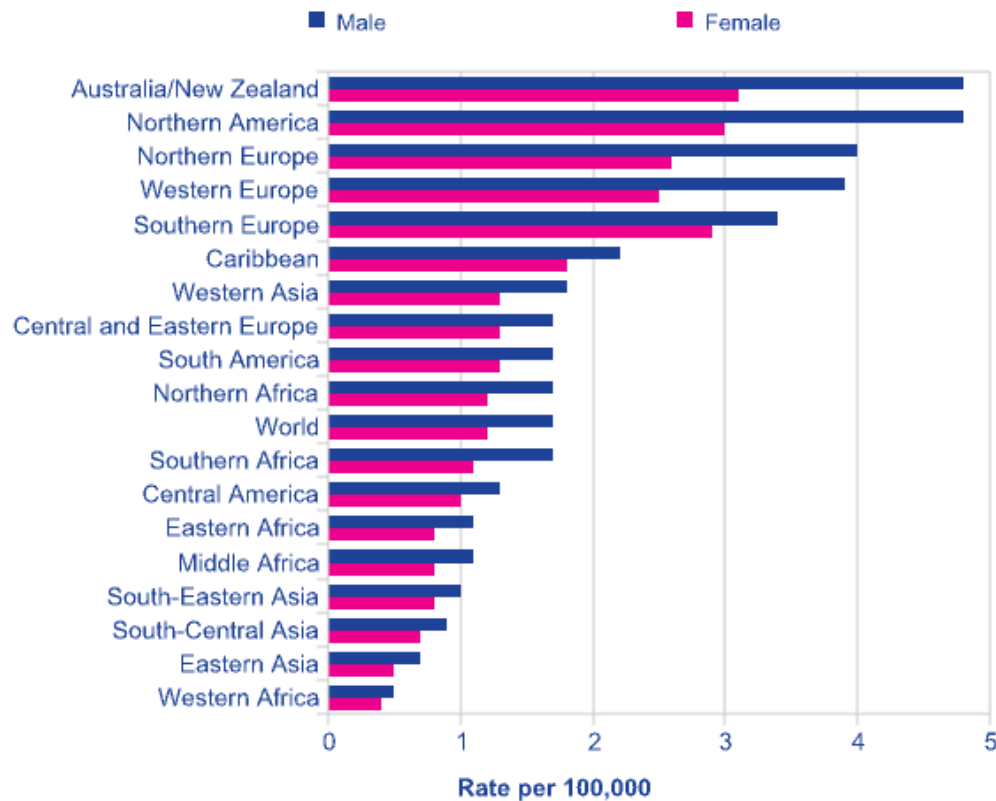


Multiple myeloma (MM): epidemiology 2



Patients with MM

Multiple myeloma (MM): epidemiology 3



Patients with MM

Multiple myeloma (MM): risk factors and etiology

- The risk of MM goes up as people age, most cases diagnosed at least after 65 years
- Men are slightly more likely to develop MM than women
- MM is more than twice as common in African Americans than in white Americans, the reason is not known
- Exposure to radiation may increase the risk of MM
- Family history
- Someone who has a sibling or parent with MM is 4 times more likely to get it than would be expected
- Being overweight or obese increases a risk of developing MM
- Having other plasma cell diseases
- People with monoclonal gammopathy of undetermined significance (MGUS) or solitary plasmacytoma may will develop MM

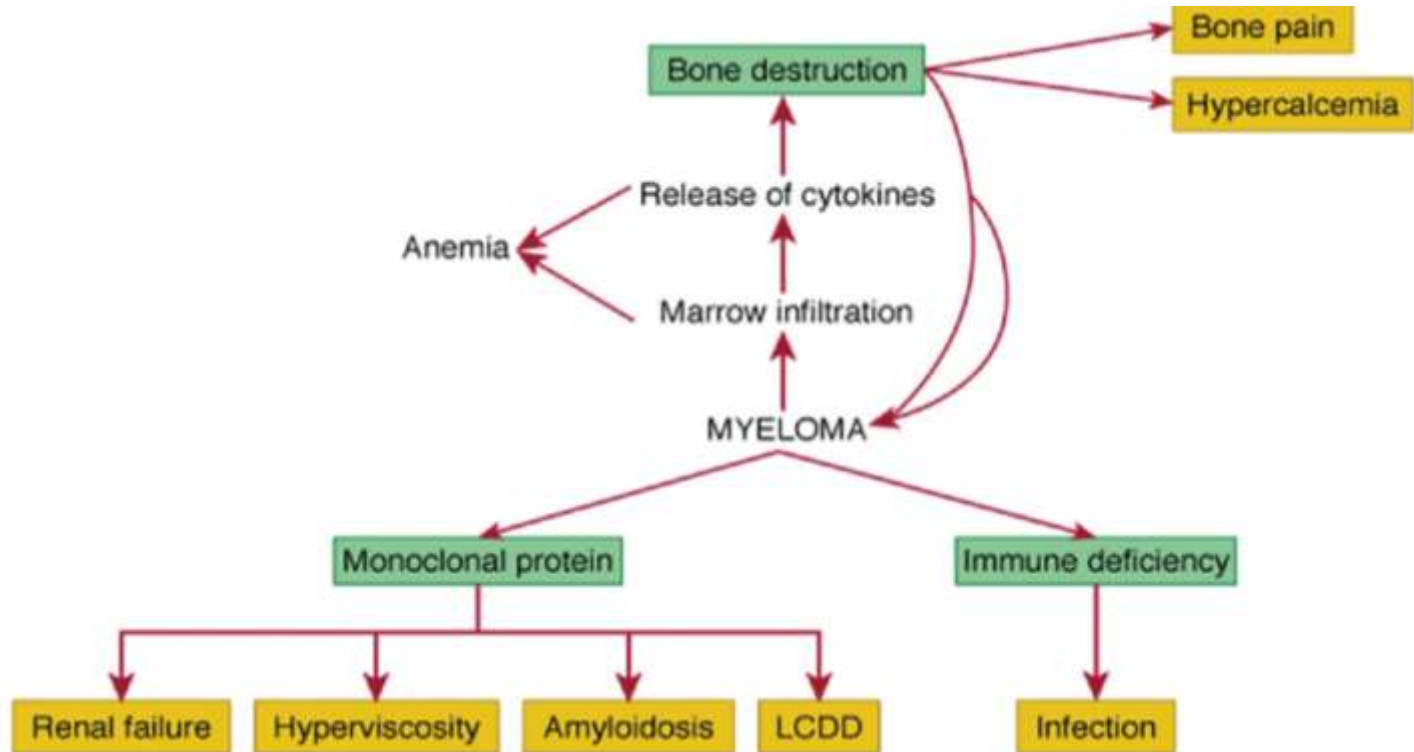
Multiple myeloma (MM): mechanisms 1

- B- lymphocytes start in the bone marrow and move to the lymph nodes
- As they progress, they mature and display different proteins on their cell surface
- B lymphocytes activated to secrete antibodies are known as plasma cells
- MM develops in B lymphocytes after they have left the part of the lymph node known as the germinal center
- The normal cell line most closely associated with MM cells is generally taken to be either an activated memory B cell or the precursor to plasma cells, the plasmablast
- The immune system keeps the proliferation of B cells and the secretion of antibodies under tight control

Multiple myeloma (MM): mechanisms 2

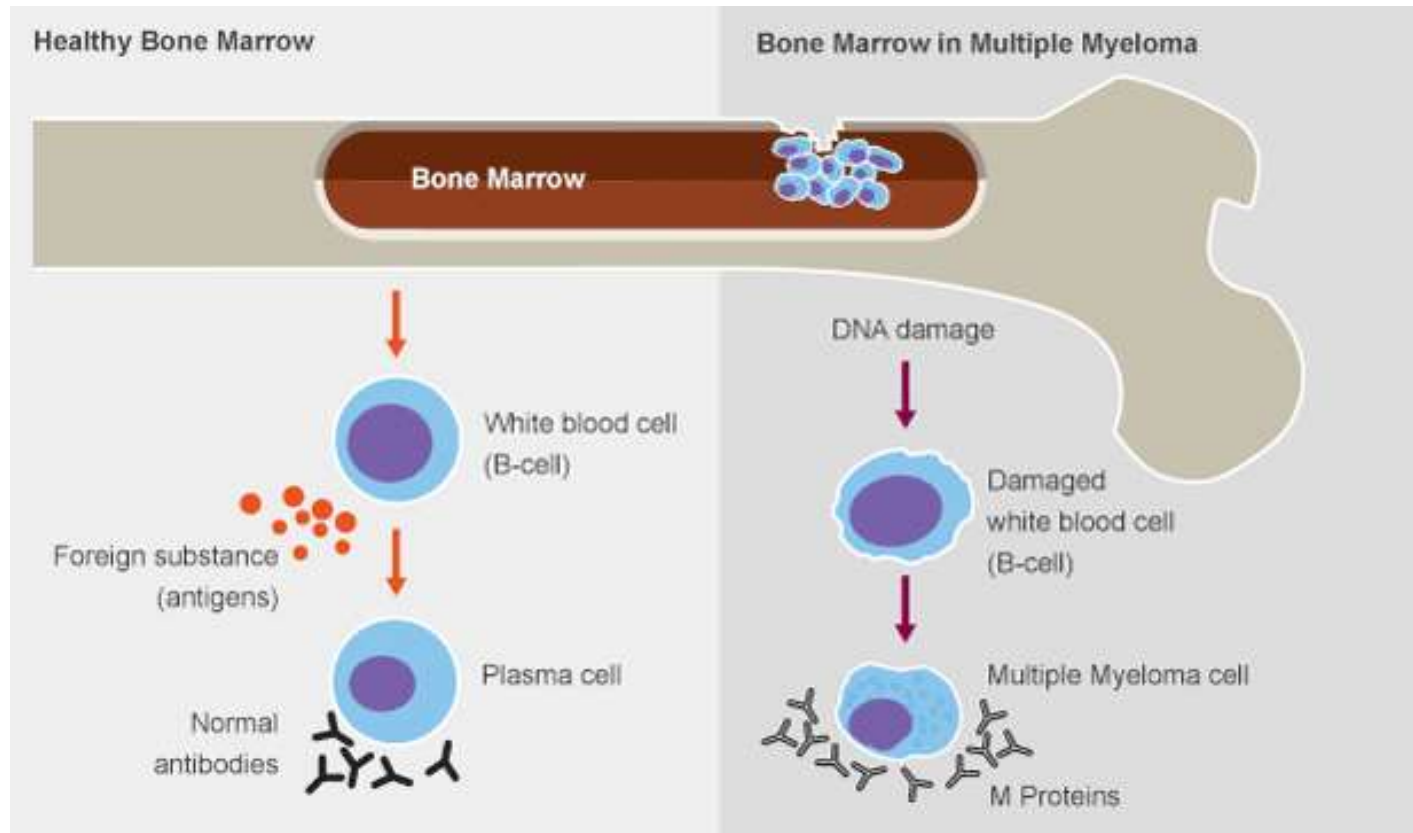
- When chromosomes and genes are damaged, often through rearrangement, this control is lost
- The result is proliferation of a plasma cell clone and genomic instability that leads to further mutations and translocations
- Production of cytokines (especially IL-6) by the plasma cells causes much of their localised damage, such as osteoporosis, and creates a microenvironment in which the malignant cells thrive
- Angiogenesis (the attraction of new blood vessels) is increased.
- The produced antibodies are deposited in various organs, leading to kidney failure, polyneuropathy and various other myeloma-associated symptoms.

Multiple myeloma (MM): mechanisms 3



Manifestations of MM

Multiple myeloma (MM): mechanisms 4



Bone marrow in MM

Multiple myeloma (MM): classification 1

International Myeloma Working Group diagnostic criteria

- Asymptomatic/smoldering myeloma: Monoclonal (M)-protein ≥ 30 g/L and/or bone marrow clonal cells $\geq 10\%$ but no related organ or tissue impairment (ROTI) (end-organ damage)
- Symptomatic myeloma: M-protein ≥ 30 g/L and/or bone marrow clonal cells $\geq 10\%$ and must have evidence of ROTI (end-organ damage) that can be attributed to the plasma cell proliferative process; manifested by CRAB (calcium, renal failure, anemia, and bone lesions: increased serum calcium ≥ 11.5 mg/100 mL; renal insufficiency [serum creatinine > 1.73 mmol/L]; normochromic, normocytic anemia with a hemoglobin value > 2 g/100 mL below the lower limit of normal or a hemoglobin value < 10 g/100 mL; lytic lesions, severe osteopenia, or pathologic fractures)
- Nonsecretory myeloma: Absence of an M-protein in the serum and urine, bone marrow plasmacytosis, and ROTI

Multiple myeloma (MM): classification 2

International Staging System

- Stage I: Serum beta-2 microglobulin < 3.5 mg/L and serum albumin ≥ 3.5 g/dL
- Stage II: Neither stage I nor stage III
- Stage III: Serum beta-2 microglobulin ≥ 5.5 mg/L

Multiple myeloma (MM): clinical presentation 1

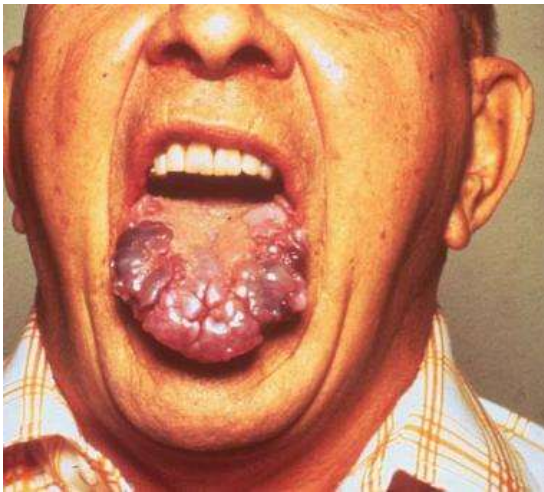
Signs and symptoms can vary and, early in the disease, there may be none. When signs and symptoms do occur, they can include:

- Bone pain
- Pathologic fractures
- Spinal cord compression (back pain, weakness, numbness, or dysesthesias in the extremities) at multiple levels
- Bleeding resulting from thrombocytopenia, and monoclonal protein absorption of clotting factors
- Hypercalcemia (confusion, somnolence, bone pain, constipation, nausea, and thirst)
- Infection through abnormal humoral immunity and leukopenia

Multiple myeloma (MM): clinical presentation 2

- Hyperviscosity (generalized malaise, infection, fever, paresthesia, sluggish mentation, sensory loss, headaches, somnolence, hazy vision, etc., when serum viscosity is greater than 4 times that of normal serum)
- Neurologic symptoms (carpal tunnel syndrome, meningitis (especially that resulting from pneumococcal or meningococcal infection), some peripheral neuropathies, etc.)
- Kidney problems, that can lead to symptoms like weakness, shortness of breath, itching, leg swelling
- Anemia, which may be quite severe
- Signs and symptoms of light chain amyloidosis (heart problems, enlarged liver and spleen, enlarged tongue, bleeding into the skin around the eyes (“raccoon eyes”),diarrhea)

Multiple myeloma (MM): clinical presentation 3



Amyloidosis infiltrating
the tongue

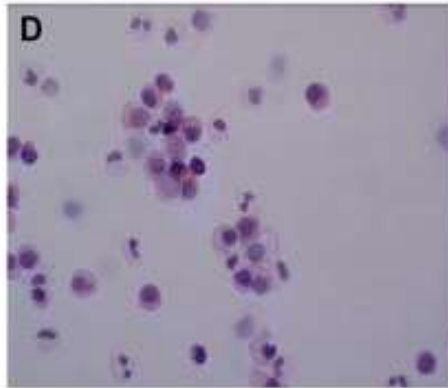


Herpes zoster
(shingles)



Swelling in the
mandible

Multiple myeloma (MM): clinical presentation 4



Cell dissemination and metastasis in MM: (A) Skeletal survey showing multiple lytic lesions in the skull (B) A PET scan showing multiple areas of enhancement, indicating that MM cells can metastasize to areas outside the BM (C) Extramedullary MM presenting as a large subcutaneous mass on the shoulder (D) Circulating tumor plasma cells, demonstrating that a small number of tumor cells are continuously circulating in the peripheral blood leading to cell dissemination

Multiple myeloma (MM): diagnosis 1

Diagnosis should be based on the following tests:

- Detection and evaluation of the monoclonal (M-) component by serum and/or urine protein electrophoresis (concentrate of 24 h urine collection); nephelometric quantification of IgG, IgA and IgM immunoglobulins; characterisation of the heavy and light chains by immunofixation; and serum-free light-chain (FLC) measurement
- Evaluation of bone marrow (BM) plasma cell infiltration: BM aspiration and/or biopsies are the standard options to evaluate the number and characteristics. Moreover, the BM sample should be used for cytogenetic/fluorescence *in situ* hybridization (FISH) studies and also has the potential for immunophenotypic and molecular investigations

Multiple myeloma (MM): diagnosis 2

- Fluorodeoxyglucose positron emission tomography is currently under evaluation but should not be systematically used
 - Complete blood cell count, with differential
 - Serum creatinine and calcium level
 - Evaluation of lytic bone lesions: a radiological skeletal bone survey, including spine, pelvis, skull, humeri and femurs is necessary. A magnetic resonance imaging (MRI) or computed tomography (CT) scan may be needed to evaluate symptomatic bony sites, even if the skeletal survey is negative and the patient has symptoms suggesting bone lesions. Moreover, MRI provides greater detail and is recommended whenever spinal cord compression is suspected
- Fluorodeoxyglucose positron emission tomography is currently under evaluation but should not be systematically used

Multiple myeloma (MM): diagnosis 3

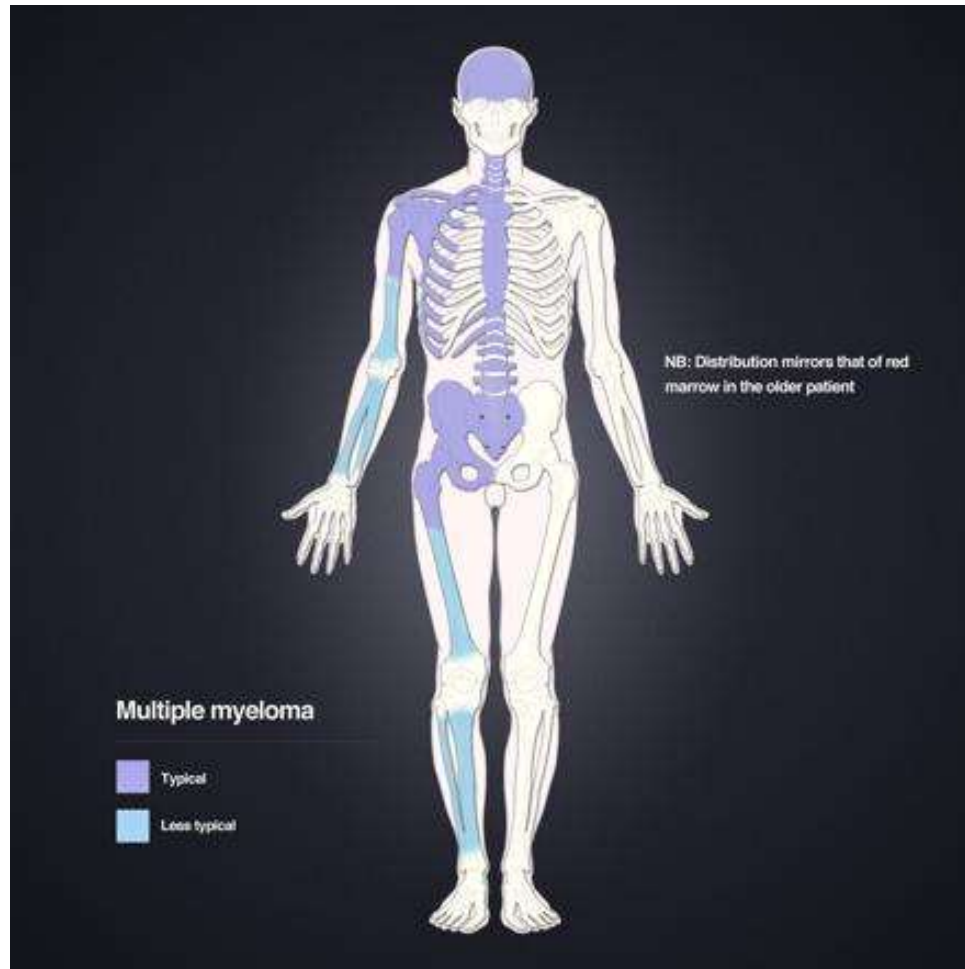
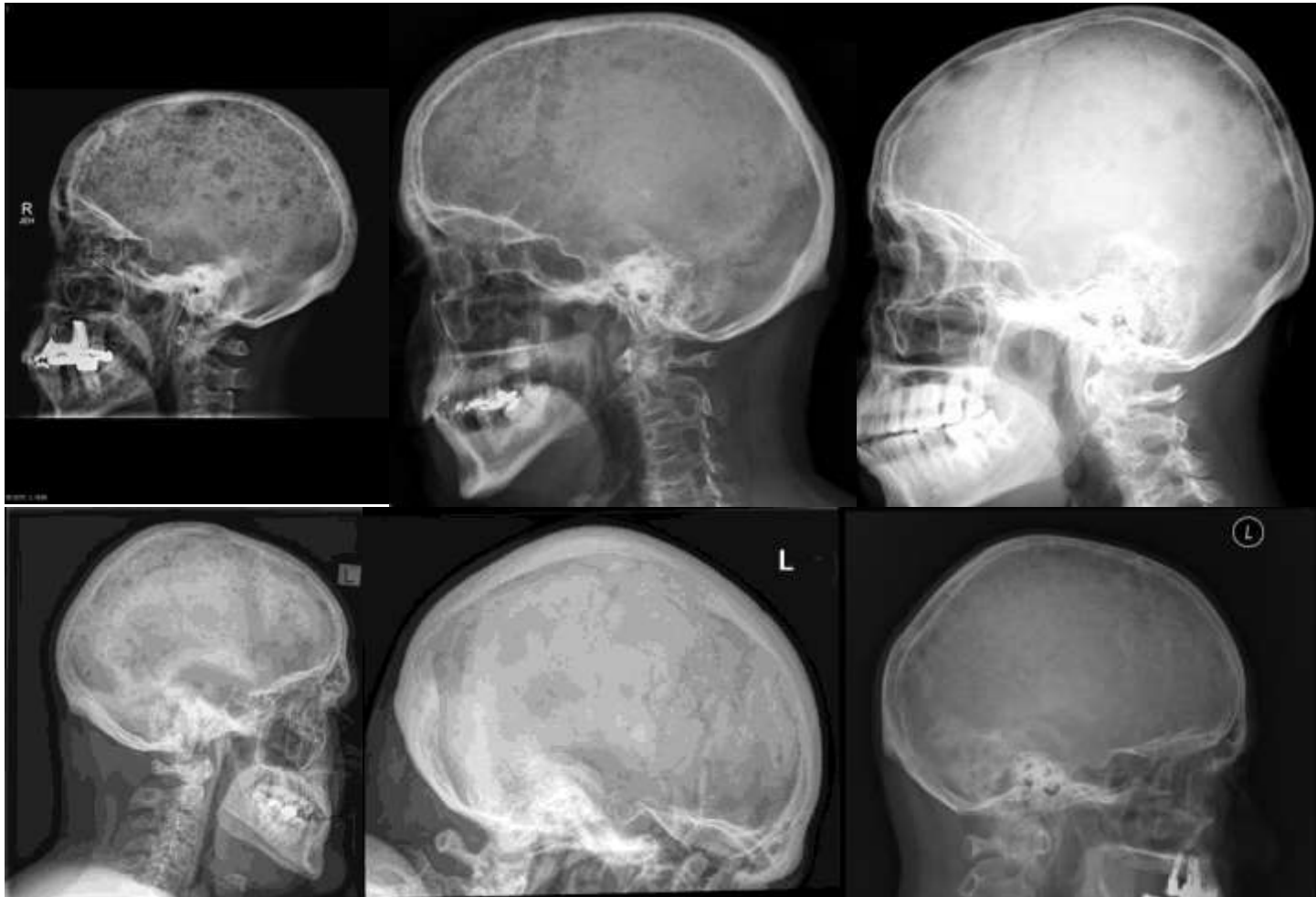
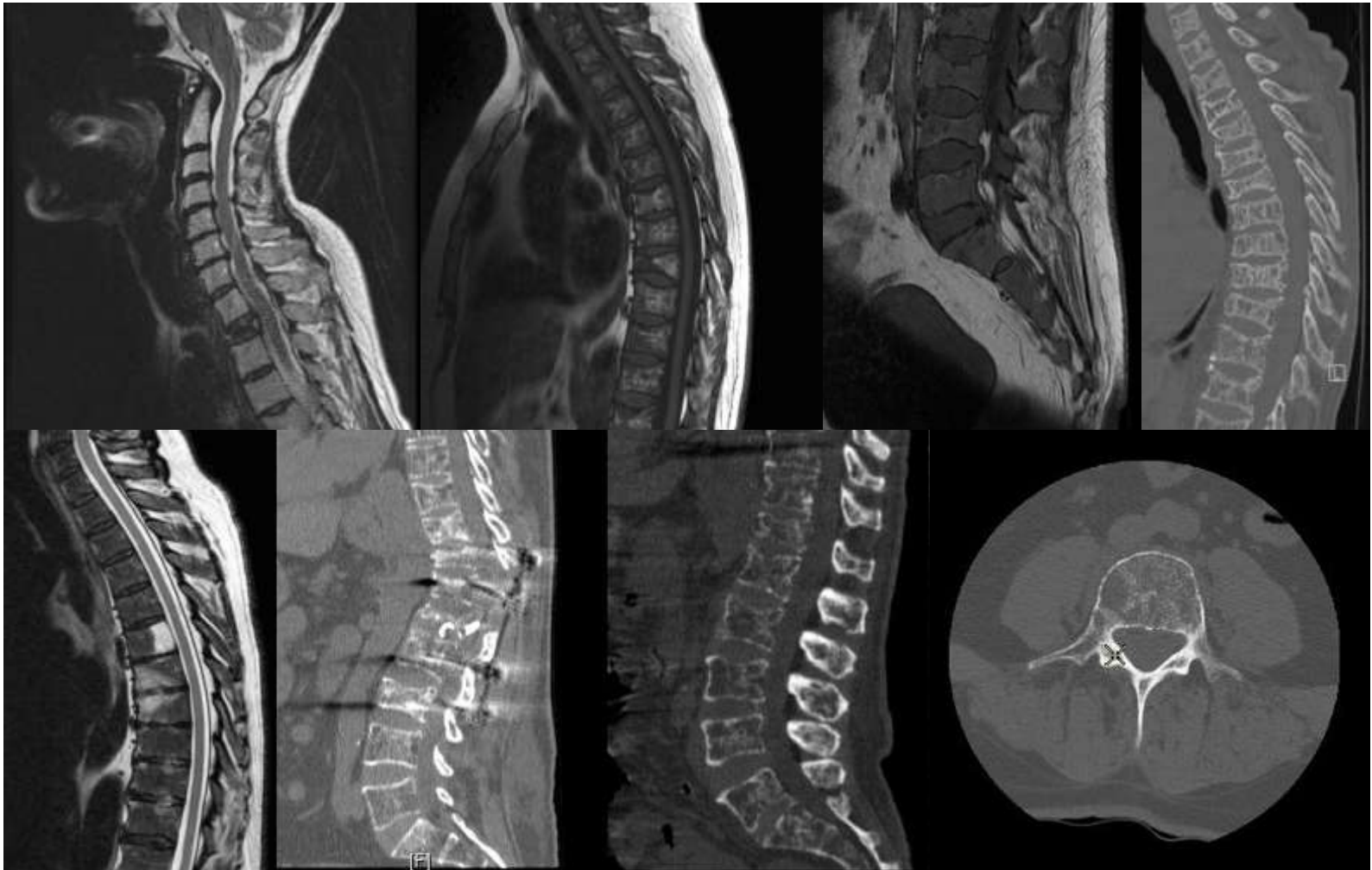


Diagram Distribution of MM

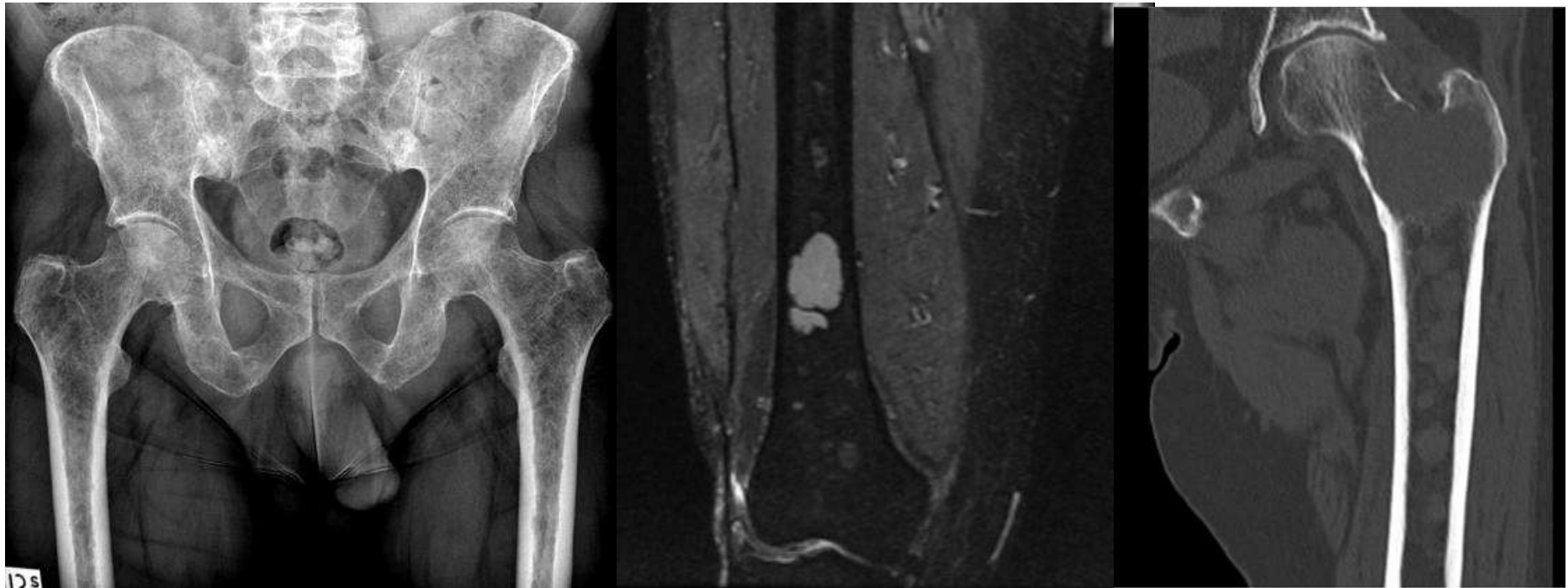
Multiple myeloma (MM): diagnosis 4



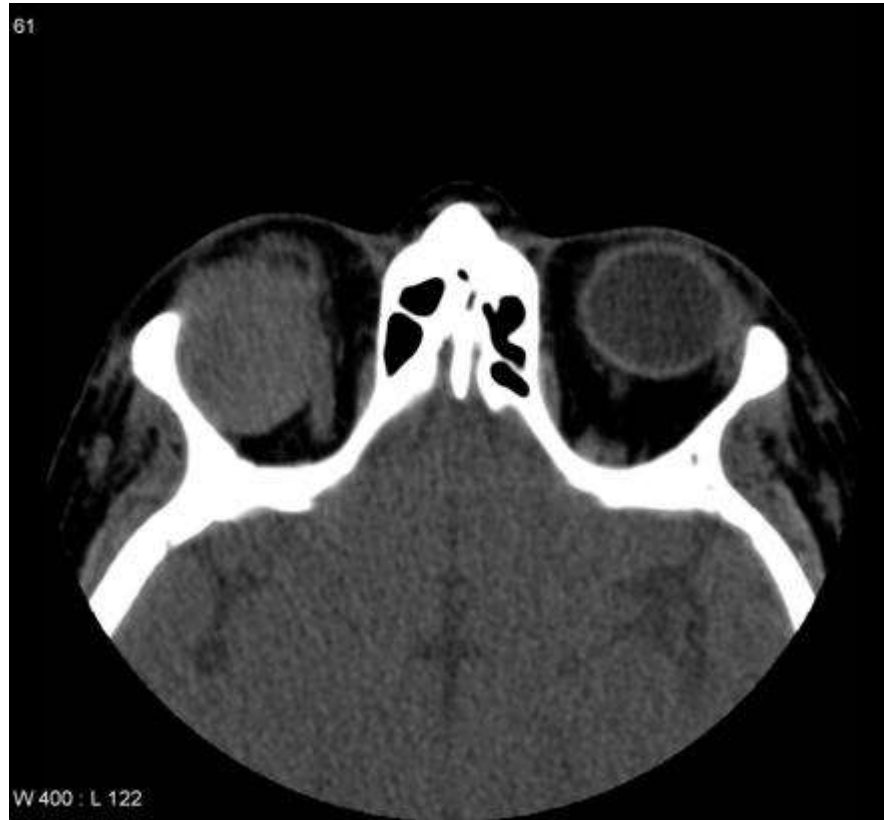
Multiple myeloma (MM): diagnosis 5



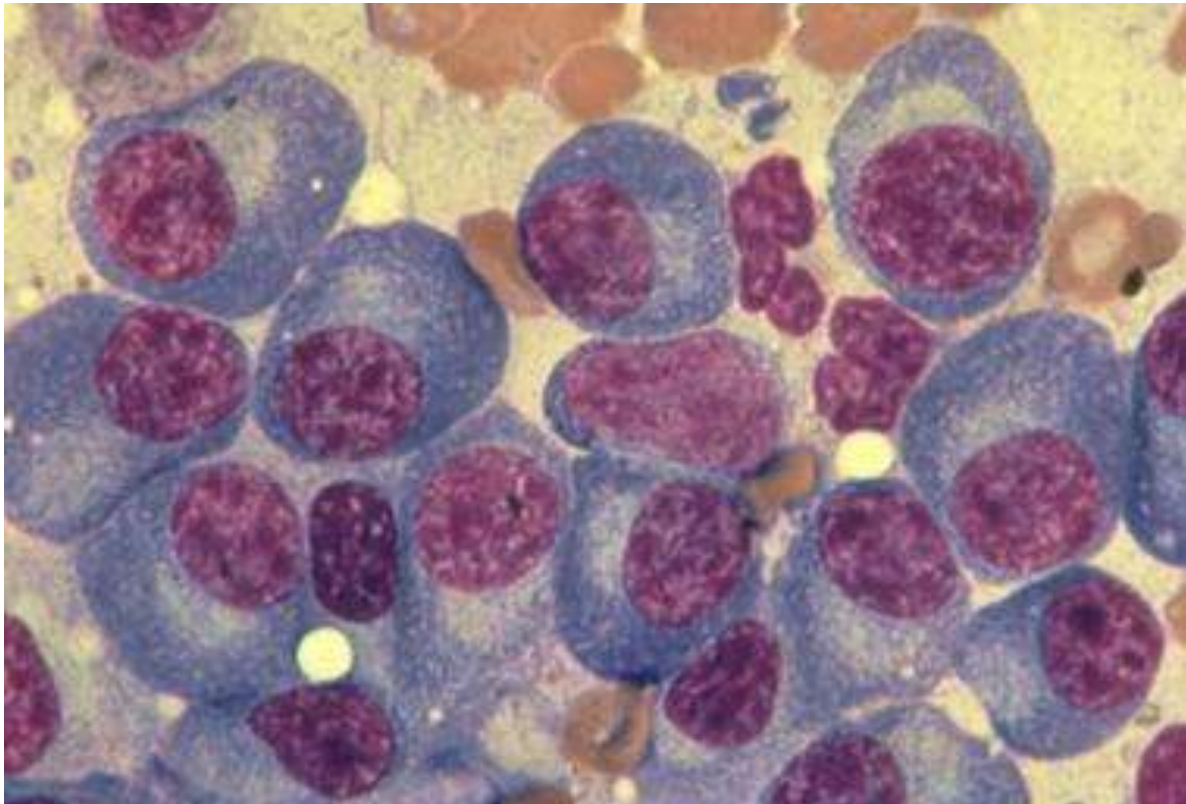
Multiple myeloma (MM): diagnosis 6



Multiple myeloma (MM): diagnosis 7



Multiple myeloma (MM): diagnosis 8

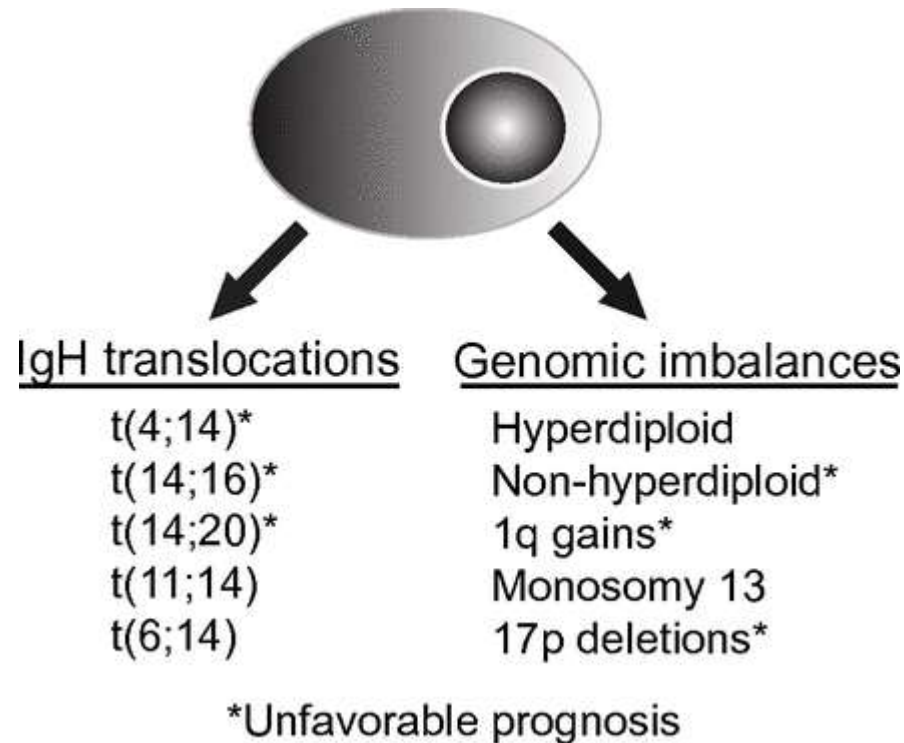


Bone marrow aspirate demonstrating plasma cells of multiple myeloma

Multiple myeloma (MM): diagnosis 9

- **Genetic testing**
- Some myeloma centers now employ genetic testing, which they call a “gene array”
- By examining DNA, oncologists can determine if patients are high risk or low risk of the cancer returning quickly following treatment
- Cytogenetic analysis of myeloma cells may be of prognostic value, with deletion of chromosome 13, non-hyperdiploidy and the balanced translocations t(4;14) and t(14;16) conferring a poorer prognosis. The 11q13 and 6p21 cytogenetic abnormalities are associated with a better prognosis
- Prognostic markers such as these are always generated by retrospective analyses, and it is likely that new treatment developments will improve the outlook for those with traditionally "poor-risk" disease
-

Multiple myeloma (MM): diagnosis 9



Genetic classifications of MM: the most commonly recognized high-risk genetic features are t(4;14) and del17p detected by FISH on either CD138-selected BM cells, or with the identification of clonally restricted plasma cells staining for cytoplasmic light chain immunoglobulin

Multiple myeloma (MM): treatment 1

- Treatment is focused on therapies that decrease the clonal plasma cell population and consequently decrease the signs and symptoms of disease
- If the disease is completely asymptomatic (i.e. there is a paraprotein and an abnormal bone marrow population but no end-organ damage), treatment is typically deferred, or restricted to clinical trials
- In addition to direct treatment of the plasma cell proliferation, bisphosphonates are routinely administered to prevent fractures
- If needed, red blood cell transfusions or erythropoietin can be used for management of anemia
- Bortezomib has the first therapeutic proteasome inhibitor approved by the U.S. FDA for treating relapsed multiple myeloma

Multiple myeloma (MM): treatment 2

Initial therapy

- High-dose chemotherapy (lenalidomide–dexamethasone, bortezomib based regimens, and lenalidomide–dexamethasone) with autologous hematopoietic stem-cell transplantation has become the preferred treatment for patients under the age of 65
- Allogeneic stem cell transplantation, has the potential for a cure, but is used in a very small percentage of patients
- Patients over age 65 and patients with significant concurrent illness often cannot tolerate stem cell transplantation, and for them the standard of care has been chemotherapy with melphalan and prednisone, with bortezomib
- Deep venous thrombosis and pulmonary embolism are the major side effects of high-dose chemotherapy

Multiple myeloma (MM): treatment 3

Maintenance therapy

- Sometimes after the initial treatment an ongoing maintenance therapy is offered
- In younger patients, maintenance therapy with thalidomide appears to increase tumor burden reduction further, which translates into prolonged progression-free survival
- Maintenance therapy with thalidomide, lenalidomide, or bortezomib is still of questionable benefit

Multiple myeloma (MM): treatment 4

- **Relapse**
- The natural history of MM is of relapse following treatment
- For patients with relapsed disease, proteasome inhibitor bortezomib is a recent addition to the therapeutic arsenal (lenalidomide, thalidomide), especially as second line therapy

Multiple myeloma (MM): treatment 5

- **Palliative care**
- Multiple national cancer treatment guidelines recommend early palliative care for people with advanced MM at the time of diagnosis as well as for anyone who has significant symptoms
- Palliative care is appropriate at any stage of MM and can be provided alongside curative treatment
- In addition to addressing symptoms of cancer, palliative care helps manage unwanted side-effects, such as pain and nausea related to treatments

Multiple myeloma (MM): prognosis

- With high-dose therapy followed by autologous stem cell transplantation, the median survival has been estimated to be approximately 5 years
- The [International Staging System](#) can help to predict survival
- The prognoses for patients with MM, as those with other diseases, are not the same for everyone: older patients often are experiencing other serious diseases, which affect survival and younger patients might have much longer survival rates

Multiple myeloma (MM): clinical case 1

Extramedullary multiple myeloma presenting as a pituitary mass lesion

- There was reported the case of a 71-year-old female patient affected by an extramedullary IgG-lambda multiple myeloma presenting as a pituitary mass lesion
- Intracellular plasmacytoma though rare, should be considered in the differential diagnosis of a pituitary mass lesion, since associated with different therapeutic and prognostic implications
- Physicians should be alert for intracellular plasma cell tumors in case of well preserved anterior pituitary function in combination with cranial nerve neuropathies and sellar destruction

Multiple myeloma (MM): clinical case 2a

Bortezomib-induced pneumonitis during bortezomib retreatment in MM

- Bortezomib is a proteasome inhibitor and is active against MM
- A 64-year-old Japanese man with MM received low-dose dexamethasone followed by bortezomib monotherapy as the initial therapy
- He had no pulmonary complications during bortezomib treatment
- Thereafter, he was treated with high-dose chemotherapy, followed by autologous peripheral blood stem cell transplantation
- Ten months after autologous peripheral blood stem cell transplantation, his disease relapsed and he received bortezomib retreatment

Multiple myeloma (MM): clinical case 2b

Bortezomib-induced pneumonitis during bortezomib retreatment in MM

- On the fifth day after the second dose of weekly bortezomib, he complained of mild dyspnea, dry cough and fever
- High-resolution computed tomography of the chest showed bilateral infiltrates with partial ground glass appearance in the lower lobes
- The diagnosis of bortezomib-induced pneumonitis was made
- His bortezomib-induced pneumonitis responded to steroid therapy and his respiratory symptoms disappeared
- So, careful management is needed during bortezomib retreatment, even after the previous course of bortezomib was administered safely

Prophylaxis

- Prophylaxis is treatment that aims to stop a lymphoma elsewhere in the body
- It can be difficult to treat once it develops, so sometimes needs a preventive treatment
- This treatment may be given as well as the usual chemotherapy for the lymphoma or may already be part of a particular regimen

Abbreviations

- CT - computed tomography
- EBV - Epstein-Barr virus
- FDA - U.S. Food and Drug Administration
- FISH -fluorescence in situ hybridization
- HCV - hepatitis C virus
- HHV8 - human herpes virus 8
- HIV - human immunodeficiency virus
- HL - Hodgkin lymphoma
- HTLV-1 - human T-cell leukemia/lymphoma virus
- IWF - National Cancer Institute's Working Formulation
- MRI - magnetic resonance imaging
- NHL - non-Hodgkin lymphoma
- PET - positron emission tomography
- REAL - Revised European-American Classification of Lymphoid Neoplasms
- RSC - Reed-Sternberg cells
- WHO - World Health Organization
- MGUS - monoclonal gammopathy of undetermined significance
- MM - multiple myeloma

Diagnostic guidelines

Europe

- [Best practice in lymphoma diagnosis and reporting](#)
- [Control of pain in adults with cancer: a national clinical guideline](#)
- [Referral guidelines for suspected cancer](#)
- [Consensus recommendations for the management of cutaneous B-cell lymphomas](#)
- [Diagnosis and treatment of primary CNS lymphoma in immunocompetent patients: guidelines from the European Association for Neuro-Oncology](#)
- [Hodgkin's lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up](#)

North America

- [NCCN clinical practice guidelines in oncology: non-Hodgkin's lymphoma](#)